Soft Neurological Signs in Schizophrenia

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Abstract

This dissertation describes a series of studies addressing the prevalence, correlates and longitudinal changes in soft neurological signs (SNS) in schizophrenia. SNS are found to be increased in schizophrenia. The increase appeared to have both a genetic and a non-genetic component. It has been proposed that SNS could be considered as one of the biological markers expressing a mediating risk for schizophrenia. In order to clarify the role of SNS in this perspective it is important to understand factors that affect the expression of SNS in a given population. Previous studies have identified possible relationships between SNS on one hand, and age, ethnicity, intelligence as well as education levels on the other. Associations with clinical features as well as cognitive function impairment have also been suggested. Antipsychotic medication side-effects appear not to be directly related to SNS, nevertheless their impacts cannot be entirely ruled out. Inconsistencies have also emerged as a result of sampling and methodological variations. The potential change of SNS with time in different phases of the disorder is another important issue that has not been adequately addressed with longitudinal studies. This dissertation describes works that addressed some of these issues in different samples using the same assessment methodology. A relatively extensive cross-sectional study addresses the relationship of SNS with demographic, educational, clinical and cognitive factors. The level of SNS in a Chinese sample is also compared with that obtained in a Caucasian sample to investigate effects of ethnicity. Data from the cross-sectional study also allow a

limited analysis addressing the contributions of age and illness duration across a wider time range. Two longitudinal studies then focus on specific phases of the disorder. The first study investigates changes in SNS amongst chronic patients approaching old age (the fifth decade). The second study addresses changes in SNS following first episode psychosis.

In the first chapter a broad introduction to methodological issues is presented. Chapter 2 continues with a more detailed review of the existing data about SNS in schizophrenia. Chapter 3 presents the core methodology and assessment instruments used in the studies. In Chapter 4 the recruitment procedures and the characteristics of the samples are described. Data analysis and results are presented in Chapters 5 to 8. In Chapter 5 important correlates of SNS are explored using data from a larger cross-sectional sample of Chinese patients and controls. These include age, gender, education level, intelligence, as well as symptom correlates of SNS. The potential effects of ethnicity were further explored by comparison between Chinese and Caucasian control samples. Additional analyses were carried out to attempt to address the relative importance of age and illness duration for SNS in patients. Chapter 6 describes in more detail the relationship between SNS and cognitive functions in this cross-sectional sample. Chapters 7 and 8 describe two longitudinal studies. Chapter 7 deals with a 3-year follow-up study for stable chronic patients. Chapter 8 addresses a 2-year follow-up study of SNS in first episode patients. In Chapter 9 the dissertation ends with a general discussion of the current findings and suggestions for key areas for future research.

Declaration

I declare that this thesis has been composed by myself and represents my own work except where due acknowledgement is made, and that it has not been previously submitted in candidature for any other degree, postgraduate diploma or professional qualification.

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The candidate was the principal investigator in all the studies reported in this dissertation. He led the research teams in the design, planning and execution of the studies. In terms of actual data collection, in study 1, 2 and 3 he personally carried out about half of the assessments. In study 4, he carried out about one quarter of the assessments personally. The data was entered and maintained by research assistants working directly under the supervision of the candidate. In data analysis, Dr Raymond Chan assisted in the performance of some exploratory analysis under the direction of the candidate. The candidate personally carried out the main statistical analysis of the data in all the studies.

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AV integration	Audio visual integration
BARNES	Barnes Akathisia Rating Scale
BPRS	Brief Psychiatric Rating Scale
CAL	Calgary Depression Scale
CNI	Cambridge Neurological Inventory
CNS	Central nervous system
CPT	Continuous performance test
DSM III	Diagnostic Statistical Manual III
DSM III R	Diagnostic Statistical Manual III Revised
DSM IV	Diagnostic Statistical Manual IV
DUP	Duration of untreated psychosis
EPS	Extrapyramdial signs
FS	Frontal signs
GAF	Global Assessment of Functioning
HEN	High Royds Evaluation of Negativity
KCH	Kwai Chung Hospital
LCKH	Lai Chi Kwok Hospital
LM	Logical memory
ICD	International Classification of Disease
MADRS	Montgomery and Asberg Depression Rating Scale
MMSE	Mini Mental State Examination
MZ	Monozygotic
NART	National Adult Reading Test
NES	Neurological Examination Scale
PANSS	Positive and Negative Symptom Scale
PYNEH	Pamela Youde Nethersole Eastern Hospital
QMH	Queen Mary Hospital
QNS	Quantified Neurologic Scores

SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
SCID	Structural Clinical Interview for Diagnosis
SIMS	Simpson-Angus Scale
SNS	Soft neurological signs
TD	Tardive dyskinesia
VR	Visual reproduction
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WAIS-R-HK	Wechsler Adult Intelligence Scale - Revised Hong Kong Version
WCST	Wisconsin Card Sorting Test
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale Revised
YBSEV	Yale-Brown Obsessive Compulsive Scale

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1 General Introduction

Introduction

This chapter provides a general background to the studies described in the dissertation. Some wider methodological issues concerning the study of soft neurological signs in schizophrenia research are discussed. A detailed review of the existing literature will be presented in Chapter 2.

General background

Schizophrenia is an important psychiatric disorder characterized by disturbance in perception, thought, language, motivation, and emotional processes. Earlier accounts were followed by the seminal work of Kraepelin (Kraepelin, 1913, cited in (1)) where "dementia praecox" was described and distinguished from affective disorders based on clinical characteristics and longitudinal course. This definition of schizophrenia as a syndrome was in anticipation of the eventual identification of an underlying neuropathological lesion. This objective still remains elusive today. In the meantime there has been various attempts to refine the definition and categorization of the disorder. Bleuler (2) in proposing the description of "the Group of Schizophrenias" have emphasized that while there may well be heterogeneity in the disorder, there exist certain "fundamental symptoms" beyond the florid psychotic symptoms. These core features are believed to be relatively specific and longitudinally stable in comparison to the psychotic symptoms. Bleuler(2) has

located the core features at a psychopathological and cognitive level (autism, ambivalence, association, affective disturbance). Although the definition and identification of the "core features" in schizophrenia has been difficult, these attempts have attracted extensive considerations from investigators exploring aetiological factors in schizophrenia. These efforts reflect the expectation that features could be identified that may act as mediators between distal etiological factors and the ultimate expression of the diagnosable clinical disorder. Subsequently various emphases have been put on features such as cognitive dysfunction, thought and language deviations, schizotypal features, etc.

Although the detailed mechanisms underlying "core features" are currently unknown, there is considerable evidence that both genetic and non-genetic factors are significantly involved. Kraepelin himself speculated that progressive and destructive processes maybe present(1). Against this background, current researches have placed much emphasis on the role of neurodevelopmental processes (3). Till now relatively few environmental causes are known, viral infection during fetal development (4-8), and peri-natal delivery complications (9), are amongst the few identified factors but their contributions are modest. The natures of genetic factors involved are also unknown, though there is some optimism that more understanding will emerge alongside technical advances in genetics research. The mode of inheritance probably involves a large number of genes each of a small effect (10;11). One implication of this mode of inheritance is that below the threshold for clinical manifestation, detectable features may be expressed (for instance, as personality traits, social

dysfunction, or neurocognitive underperformance).

The concept of such "target features" has been reviewed, amongst others, by Tsuang (12). "Target features" encompasses the idea that genetic and non-genetic processes lead to maldevelopment in neurocognitive systems. These abnormalities then interact with brain maturational processes and environmental factors in determining the onset of psychosis. It is also acknowledged that neurodegenerative processes may also be involved after the onset of illness. In recognition of the possible aetiological heterogeneity of schizophrenia, it is expected that target features are multiple and heterogeneous. According to this account target features should be present in at-risk individuals from childhood; it may be modified during development and particularly at the time around illness onset. Putative subsequent degenerative processes might also modify these particular target features. Target features should be increased in relatives of patients but perhaps not to a similar extent. In addition, the manifestation of multiple genes of small effect would lead to an expectation that target features should be present (but not to the same extent) in the general population.

Many candidate target features have been suggested for schizophrenia. Apart from soft neurological signs, other features include measures of attention (13), neurocognitive function (14;15), eye movement disorder (16), and personality traits (17).

Soft neurological signs

In the past decades, soft neurological signs (SNS) have been described and studied in schizophrenia and a number of other psychiatric disorders. This dissertation describes a series of work targeting the characterization of SNS in schizophrenia. In particular, the focus will be on the study of change in SNS over time, as well as various correlates of SNS in clinical, demographic and neuropsychological domains.

Historical notes

Some of the earlier applications of soft neurological signs were associated with the observation that a number of signs appeared to be present early in the course of normal childhood development, before they disappear by adulthood (18), some of these signs re-emerge later under pathological conditions. They have often been considered under the concept of a "release phenomena". In explaining these release phenomena it has been postulated that brain functions are organized in a hierarchical system, in which ontologically earlier functions are more at the "core" and less susceptible to disintegration caused by later illness. During the course of development, these earlier manifestations are subsequently inhibited by the emergence of later functions. In pathological situations the later functions are more vulnerable to disintegration. When they are disabled by illness, their "inhibiting" effects on the earlier functions are nullified, leading to the re-emergence of an earlier function. Explanations such as these have often been employed to account for the appearance of primitive reflexes in patients with frontal lobe lesions. In considering

soft neurological signs it is necessary to supplement this view with a developmental perspective that some of the earlier signs remain expressed because the later functions fail to develop fully due to a developmental anomaly. In this context, early investigators of childhood development have been interested in the expression of SNS in various childhood clinical conditions.

Since SNS expression involves mutual modulation of normal functions, variation in individual expression is expected. In general the difference in SNS between a healthy population and a clinical population lies more in quantity than in quality. This is in notable contrast to some other categories of neurological signs (e.g. dyskinesia, which are primarily present only in pathological conditions). As such it is important to note that SNS are very much quantitative variables to be measured, rather than merely observed to be present. The fact that SNS are present in the normal population discourages expectations that SNS could be highly specific in relation to clinical diagnosis.

Nature and boundaries of soft neurological signs

Signs in clinical medicine

Conventionally, "signs" and "symptoms" constitute the basic clinical manifestations of a disorder. Whereas symptoms are reported by patients, signs refer to observations that could be evaluated "objectively" by the clinician. In clinical medicine, "signs" ranges from simple passive measurement (such as a skin mass) to observations of

responses that are made using a standard testing procedure (such as blood pressure, or tendon reflex). In contrast to symptoms it is assumed that expressions of signs are usually not under voluntary control of either the subject or the observer.

Unique features of central nervous system (CNS) signs

Disorders of the central nervous system produce signs of a more complex nature. In CNS disorders elicitation of signs often requires the subject to carry out behavioural responses. While some CNS signs, particularly those of the primary motor and sensory systems are less open to voluntary control; many other signs of higher CNS function involves cognitive processes that are more difficult to shield from motivational or voluntary factors.

In addition, the nature of higher CNS signs is likely to be more "integrative" (i.e. involving coordination of a number of lower level units each of which is functionally independent). An example (non-soft sign) is "apraxia", the sign is only considered valid when the basic motor system is intact and yet the subject failed to carry out more complex motor sequences. It is expected that such higher level signs are more affected by various cognitive and motivational processes and merge with more systematic neuropsychological test paradigms. It is important to note that as the assessment of SNS are more open to cognitive and motivational factors, it raised the possibility that illness processes may indirectly affect the assessment of soft neurological signs through these variables. Despite this concern, it is noteworthy that reliable assessment of SNS has been achieved with patients with psychotic disorders

(see below).

Soft neurological signs and extrapyramidal signs

Among CNS signs, a further group merits particular consideration in relation to their significance in psychotic disorders. This group of signs is also present in conditions affecting the basal ganglia system (e.g. Parkinson's disease, Huntingdon's chorea, Wilson's disease). They are commonly considered under extrapyramidal signs (rigidity, tremor, bradykinesia, dyskinesia, dystonia and akasthisia) (19). It is recognized that they are often accompanied by cognitive and subjective symptoms (20). Previously it was assumed that they were largely consequences of antipsychotic medication. Recent studies in medication-naïve patients have however shown that extrapyramidal signs were present in patients never treated with medication, and that the extent of their presence may be similar to patients treated with medication (21-26). These studies suggested that spontaneous extrapyramidal signs might be an expression of the core illness process. In this context, imaging studies have also suggested that patients with extrapyramidal signs might have increased ventricular sizes (25;27). As extrapyramidal signs are conventionally conceptualized as being distinct from SNS and are usually studied separately from SNS they will not be the focus of the current dissertation.

Soft neurological signs and neuropsychological paradigms

The boundary between neuropsychological tests and soft neurological signs also

requires consideration. Traditionally these are two independent approaches originating from different disciplines and theoretical positions. Soft neurological signs evolved within the medical tradition of identifying "signs" accompanying disorders, and as such, carry with them a "bedside" characteristic (that the tests are relatively simple, portable, brief, and can be carried out with minimal additional tools). These characteristics have influenced the development of SNS.

In contrast the neuropsychological approach aims at designing sensitive and specific test paradigms to capture brain system dysfunction in an objective manner (28). The ultimate aim is to relate test performance to macroscopic brain structure abnormality. Neuropsychological assessments involve more use of instrumentation (whether digital or not), and make more extensive use of specially designed stimulus sets.

These two approaches run in parallel in many study of psychiatric disorders. With the development of standardized assessment procedures, soft signs assessments have evolved to be more akin to neuropsychological testing. While there have been a few comparison studies, relationship between SNS and neuropsychology has not been extensively addressed. Past studies have at times incorporated items of neuropsychological nature into SNS batteries. At other times, neuropsychological performance was compared with SNS to identify correlation patterns. In either case, it is important that studies address the degree of overlap and non-overlap between these two domains. Areas of non-overlap may indicate involvement of different neural systems. Knowledge of areas of overlap is also practically useful as signs are

far more economically assessed than neuropsychological tests. Thus if a sign and a neuropsychological test carry comparable information value, it is probably more cost-effective to measure the former rather than the latter.

Measurement issues

Standardization of measurement

Soft neurological signs are numerous; many of the signs were originally described in less accessible sources (Appendix 4). As they do not constitute part of an obligatory clinical examination (because the significance of their presence is less distinct), they do not have the advantage of propagation through standard textbooks on clinical examination. Furthermore the inclusion of items within soft signs scales originated from different research efforts with considerable dispersion in time and space. Intense deliberations over their theoretical constructs and empirical findings have been relatively limited. Finally it is important to recognize that compared to conventional neurological signs, SNS are more open to a variety of cognitive factors. Therefore the exact manner of elicitation (for instance, the exact instruction given) could conceivably have an effect on the performance. In this context, operationalization of soft neurological signs has been gaining increasing acceptance among research groups. Substantial progress has been made since the early compilations of partially overlapping instruments from different groups (which contained relatively little detailed description of the elicitation and scoring for individual items). Operationalization of the method used for the elicitation and

recording of individual signs (29-31) has helped to reduce procedural variations.

Reliability and Validity issues

In general, standardization of an assessment procedure enhances the reliability of the measurement as it reduces observer and other sources of variance. However in the assessment of complex phenomena, there may be an inherent limit to what can be defined explicitly. A trained human observer makes subtle (implicit) adjustments to the assessment in such a way that the phenomena under observation can be highlighted. These subtle adjustments often cannot be explicitly operationalized. This freedom is restricted with the use of standardized instruments. Such problems with structured assessment are expected to have particular impact in the assessment of "frontal lobe" phenomena, as it is recognized that some features of the latter are best manifested in a low-structure, spontaneous setting. An example is that patients with strong tendencies towards imitation and utilization behaviour in a spontaneous setting nevertheless may not exhibit the corresponding signs in a structured assessment procedure (my clinical observation). Thus standardized assessment in this case would lead to a false negative finding. It is relevant that in a large number of psychiatric conditions, the putative site for psychopathology involves functions of the frontal lobes. The cost of standardization in the assessment of neurological signs in psychiatric condition is an issue that needs to be addressed in future studies. Nevertheless, for the works addressed in this dissertation, the advantages of using standardized assessment appear to out-weight their limitations.

Dimensionality of measurement

Many data analysis procedures require the phenomena under investigation to be graded along a dimension. A common consequence of quantification is the compression of complex phenomena consisting of a number of dimensions into a single linear dimension. For instance, a symptom which comprises a number of partially independent dimensions (e.g. hallucination has the dimension of frequency, intensity, vividness etc) is nevertheless coded by a single severity score in many symptom-rating scales. Algorithms for reducing the complex phenomena into a single dimensional score need to be clearly specified in order to resolve conflicts between different dimensions. Modern SNS rating scales only partially address this issue (see below).

Quantification of SNS

Quantification of SNS would require that it is meaningful to describe a sign as having an ordered grading in severity. That is, there are instances of manifestation that could be said to be "more serious" than others. To consider an example, in "finger thumb tapping" the subject makes regular tapping movement using the thumb against the index finger. When the sign is "mild", movement is on the whole smooth, apart from the occasional error. When the sign is "severe", there is almost a complete breakdown of movement. It is usually not problematic to make comparison between these two extremes. The difficulty however becomes more apparent if the manifestation falls in the intermediate spectrum between these two poles. For

instance, the subject could follow the movement but only at the expense of an overall slowing. If asked to speed up the subject might make inaccurate taps where the thumb and index fingers misses each other. To complicate the matter, there is more than one way of being inaccurate. One could miss the contact (spatial inaccuracy), or one could miss the rhythm (temporal inaccuracy). Depending on the strategy used by the subject, there may be a tradeoff between these two dimensions. It would be difficult to assert *a priori* that spatial inaccuracy is more severe than temporal inaccuracy, or vice versa. Currently not enough is known to render it practicable to devise a conversion factor between the two performance dimensions. Future studies that examine each signs individually may address some of these issues. In any case, one solution is to use a rating scale with a small number of possible scores, so that all intermediate situations are described by one score, thus avoiding the necessity to make comparisons between them. One alternative approach is to elicit the sign in such a way that performance along one dimension is fixed, for instance, the rate of tapping can be paced so that the subject is instructed to keep to the pace regardless of whether the fingers make contact with one another. Such afford is only partially successful and examples are to be found in certain standardized instructions given to subjects.

Subgrouping of SNS

The issue of whether signs belong to natural groups is a difficult question to address. The usefulness of categorization depends on the level of details considered. At higher

resolution, each sign can be regarded as a category on its own. At lower resolution all soft signs could be summarized under one single category. Between these two extremes there are a number of ways to classify soft signs. It is important to realize that the bases for these classifications are usually *a priori*, and come largely from theoretical considerations. (The common basis on which subgrouping are made are discussed in Chapter 2)

When signs are grouped together into subgroups it is pertinent to consider how the item scores should be treated to yield a subgroup score. One important issue is whether one treats the *number* of positive signs and the *severity* of each sign as convertible (i.e. whether the presence of a single sign scored "two" can be considered as equivalent to the presence of two separate signs, each scoring "one"). In addressing this problem, there is currently not much empirical guidance. One way to avoid the above reduction of information is to use the number of positive signs (regardless of the severity) as a measure in constructing the subscale scores. This is the approach adopted in this dissertation.

2 Soft Neurological signs in schizophrenia: a review

In this chapter, key findings involving soft neurological signs in schizophrenia are reviewed and discussed.

The review starts with a consideration of the evolution of SNS research from the early studies to the more recent research studies, with notes on how the definition, categorization and application have changed. Major empirical findings are then reviewed. The prevalence and specificity of SNS in relation to schizophrenia is first considered. This is followed by data on SNS in relation to at-risk groups and a discussion of the demographic and clinical correlates of SNS. Finally the review ends with a consideration of data on the relationship between SNS and cognitive function.

Concepts and overview

Early studies of SNS in childhood

Systematic studies addressing soft neurological signs in schizophrenia appeared in the 1960's. SNS has initially been more widely applied to the study of childhood disorders. In one of the earliest accounts, Bender described the presence of "characteristic disturbances in patterned motor behaviour" and "primitive reflex patterned activities that outlived the stage to which they belong" in a study of "childhood schizophrenia"(32). Though the nosological status of "childhood schizophrenia" was subsequently challenged, soft signs were considered relevant to the studies of learning difficulties as well as the then evolving concepts of "minimal

brain dysfunction" and "hyperactivity".

Adams et al (33) reviewed studies of soft neurological signs in relation to children with learning disability. They pointed out that up to that time many studies of SNS have been conducted non-systematically but the studies are poorly controlled and there is a lack of normative data. At the time, soft neurological signs were broadly defined by some authors as "those neurological variations that are equivocal or intermittent". Amongst these studies, Denhoff (34) suggested a positive relationship between diadochokinetic signs and school performance. Importantly, Grant (35) pointed out diadochokinetic ability did not fully develop until 9 to 10 years. Rutter (36) also noted the association between choreiform movements, hyperkinesis, and learning problems. Association of finger agnosia (a skill which matures in late childhood) and dyscalculia in the context of developmental disorder has also been well described.

Adams (33) studied 368 10-year old normal children and children with learning disability in relation to the following set of neurological signs (eye-hand preference, balance, stereognosis, graphesthesia, choreoathetosis, finger localization (agnosisa) and diadochokinesia). They concluded that amongst these signs diadochokinesia and graphesthesia were most discriminating between normal and learning disabled children. However, the magnitude of the difference was modest and the groups cannot be readily discriminated solely on the basis of SNS. Landman (37) studied SNS in children and noted that SNS are associated with impaired school performance.

However they also pointed out that SNS are also present in normal functioning students. Study in preschool children revealed no relationship between the presence of SNS and cognitive dysfunction, linguistic abilities, memory or thinking. However since some of the SNS are not fully developed till late childhood, their application to the preschool age group might have compromised the findings.

Shaffer (38) compared adolescents at the mean age of 17 between those known to have had exhibited SNS at age 7 and those that did not have SNS at age 7, and found that the former group had lower IQ and more depressive symptoms, withdrawal, and anxiety at age 17. There was no relationship with attention deficit or conduct disorders. Most of the variance was accounted for by SNS independently of IQ. This study focused on psychopathology other than schizophrenia as the age of the study group did not extent to the peak onset age for schizophrenia. SNS as an expression of risk for schizophrenia will be discussed in sections below.

Early application of SNS to schizophrenia

Amongst early accounts of SNS in schizophrenia, Meehl (39) suggested the consideration of soft signs as indicators of "neurointegrative deficit". Fish (1963, cited in Erlenmeyer-Kimling (40)) viewed soft signs as a measure that reflects developmental dysregulation in high-risk individuals who subsequently developed schizophrenia spectrum disorders. Rochford (41) also suggested that SNS should be viewed as indictors of non-specific diffuse CNS dysfunction "denoting deviations in neurological organization reflected in impaired cognitive functions, decreased ability

to control attention, impulse and motor functions in varying combinations".

In a similar vein, Quitkin (42) employed soft neurological signs as indicators of "Central Nervous System damage" in a study that attempted to demonstrate that schizophrenia associated with poor pre-morbid adjustments has an "organic" basis. Using SNS as a maker, the study revealed that schizophrenic patients with poor pre-morbid adjustment had increased SNS, in contrast to patients with other forms of schizophrenia. It is thus apparent from the early stages of SNS research in schizophrenia that SNS was conceived as (1) an "integrative" (rather than primary sensory or motor) deficit, and (2) an indication of organic CNS dysfunction.

Shaffer (43) reviewed the then available literature and distinguished between two groups of signs: those that are non-localizing but can be elicited reliably, and those that cannot be reliably detected (e.g. reflex or tone asymmetries). Since this pivotal distinction was made, the study of SNS has largely been able to focus on the first group. The emphasis on reliability has enabled SNS to evolve as a robust and legitimate "target feature" in further studies. It has also paved the way for subsequent refinement by the use of operational criteria.

Theoretical issues in SNS

SNS as frontal dysfunction

In the context of investigating neuropsychological impairments associated with frontal lobe dysfunction, Luria (44) described a set of neurological signs (fist-edge-palm, Ozeresky sign etc.) which had subsequently been included in many soft neurological signs batteries. In some batteries these signs are grouped together as a distinct subscale (e.g. complex motor sequencing in NES). The study of Cox (45) exemplifies a common approach at the time. While acknowledging the non-localizing nature of SNS, soft signs were nevertheless grouped according to putative primary brain systems involved. "Frontal" signs included the grasp reflex, palmomental reflex, "conceptualization" (L/R hand signaling in response to upper and lower stimulus), visual perseveration of spoken commands, tendency to mirror movement after examiner demonstrate movement, left-right disorientation, and word-list learning. "Parietal" signs included complex motor acts (tying shoelaces), imaginary acts, oral "apraxia", tactile discrimination, extinction, two-object test, and stereoagnosia. "Temporal" signs included memory, nystagmus, face drawing, recognition of missing parts, and rhythm tapping. "Occipital" signs comprised visual field deficits and optic agnosia. The inclusion of frontal signs was different from those selected by other researchers (e.g. complex motor sequencing in Heinrich and Buchanan (46)). Some of the tests involved are more often considered as cognitive function proper (e.g. memory, drawing, conceptualization). The potential blurring of boundary between SNS and cognitive function was highlighted in this study and this

theme has persistent up to some of the more recent studies. Some issues concerning the boundary between SNS and neuropsychological function have already been discussed in Chapter 1.

SNS as motor dysfunction

Manschreck (47) discussed a wide range of voluntary motor disturbance in schizophrenia. They broadly categorized motor disturbance into those that are spontaneous and those that are elicited. Motor soft signs are included in the "elicited" subgroup. In addition they also included some sensory integration soft signs (agraphesthesia and astereognosis). Manschreck's approach highlighted a broadening of perspective in viewing SNS in the context of a wider range of movement disorders. This is an approach that has subsequently been taken up by several investigators but would deserve more systematic exploration.

SNS as indicator of complex neural system dysfunction

In Woods (48) the meanings of hard and soft signs were contrasted. Hard signs are proposed to reflect localized damage whereas soft signs are considered as reflecting *functional dysconnection* between cortical and subcortical systems (30;49;50). A further hypothesis relates signs to presumed aetiological factors, neurological signs are categorized into "focal" or "integrative" signs (51). "Focal" signs are postulated to be prevalent in sporadic cases whereas "integrative" signs are expected more in cases with family history and in their first-degree relatives.

SNS as target features

As mentioned, the general role of SNS in schizophrenia research can be summarized as in Tsuang's model of "target features" (12). SNS was conceptualized as one of the features that potentially have relevance in addressing etiological factors. The concept of target features was elaborated as "clinical or neurobiological characteristics that are expressions of the underlying predisposition to the illness'. The model considers illness as resulting from multiple genetic and environmental variables that may be additive or interactive. These variables act upon three stages: neurodevelopment, later adolescence (around onset), and after onset of psychosis. This model accommodates etiological heterogeneity by postulating that if a relatively small number of variables out of a large possible pool are sufficient for expression of the illness, then a wider range of different permutations of underlying variables could be associated with illness manifestation.

Subgrouping of SNS

Different research groups have attempted a number of subgrouping schemes for SNS. Some of these were based on the nature of the signs, some were based on putative brain systems involved, and some were based on statistical clustering of signs. Heinrich and Buchanan (46) in reviewing a larger number of earlier studies have arrived at a more widely adopted subgrouping of soft signs. They grouped together signs such as extinction, astereognosis in the area of "integrative sensory function". These are "integrative" function in the sense that their impairments are demonstrated

against a background of intact primary sensory functions. Motor coordination consisted of signs such as finger thumb opposition, dysdiadochokineses and mirror movements. Once again, they are present despite the intact functioning of muscle strength and reflexes. A further group, sequencing of complex motor acts, have been proposed. These signs included the fist-edge-palm, the fist-ring test and the Ozeretski test (adopted from Luria (44)). All of these assessed the subject's ability to perform regular repetitive alternations in hand positions.

The boundary of items between complex motor acts and motor coordination has not yet been thoroughly considered. More detailed comparison would suggest that, similar to the complex sequencing subgroup, a number of signs in the motor coordination subgroup also involve repetitive alternation in hand positions (finger thumb opposition, dysdiadochokineses). The difference between these and Luria's signs appears to be a matter of quantity (the number of elements in a repeat sequence) rather than quality. On the other hand, signs such as primitive reflexes and mirror movements did not involve movement sequences and might have different significance.

In the Cambridge Neurological Inventory (29), this subgrouping was further refined, motor coordination included all signs that involve repetitive sequencing. Sensory integration remained unchanged. A new category, "disinhibition signs", included those signs that involved manifestation of spurious movements in a time and place where they were not expected.

Factor analysis of SNS rating scales

One approach to studying the structure of neurological signs is to conduct factor analysis based on empirical data using structured examination scales. Several authors have attempted factor analysis of items on SNS rating scales.

Schroder (52) has performed factor analysis on a SNS scale and found that Luria-type frontal signs (FS) loaded in motor coordination and complex motor acts and are partly independent of other neurological signs which contributed to 4 other factors. Malla (53) also attempted factor analysis of NES data from 100 schizophrenic patients. The result yielded 5 factors, which the authors identified as sensory integration, motor integration, motor coordination, sequencing planning, and extrapyramidal signs. Disappointingly, the correspondence to conceptual item classification was only modest. Finally, Krebs (54) constructed a new SNS scale in which factor analysis yielded 5 different factors, namely, motor coordination, motor integrative function, sensory integrative function, involuntary movement or posture, as well as quality of lateralization.

There are a number of difficulties associated with attempts to factor analyze items in SNS scales. Firstly for most individual items, the prevalence of positive score is usually relatively low (below 10 or 20 percent). This results in a significant skewing of data towards zero and renders the item less suitable for inclusion in factor analysis (which ideally requires for continuous variables with a normal distribution). The quantification of severity for an individual item is also problematic as often the rating

is given for a dichotomous (present, absent) or 3-category (absent, present, severe) classification. The large number of items usually included in SNS scales also necessitates a large sample size for proper factor analysis, i.e. a ratio of variables to subjects of 1:10 (55). This has seldom been achieved (for instance the ideal sample size for factor analysis of a scale consisting of 50 items would be around 500).

SNS in schizophrenia

Prevalence

Heinrichs and Buchanan (46), in reviewing 25 years of research on SNS, noted that without exception SNS are increased in schizophrenia. They emphasized that despite their non-localizing nature, SNS are reliably elicited by standard procedures. They highlighted that despite different diagnostic criteria being used in these studies, findings across the time periods yielded largely similar results i.e. that SNS are increased in schizophrenia.

Specificity

Apart from being increased in schizophrenia, soft neurological signs are present in the normal population and in other psychiatric conditions. Their presence in other psychiatric disorders may shed light on common etiological features shared by the disorders. The main questions are firstly, whether SNS are also increased in other psychiatric disorders such as affective disorder, anxiety disorder and personality disorders, and secondly, whether the increase is to a similar extent as in

schizophrenia. Currently most of the available data address SNS in affective disorder.

SNS in affective disorder and schizophrenia

Studies which could address the specificity of SNS to schizophrenia relative to affective disorders up to 1986 was reviewed by Heinrich and Buchanan (46). In the majority of the studies, SNS were found to be significantly increased in schizophrenia relative to affective disorder (41;45;47;56-61)

In the study of Rochford (41) SNS in patients with schizophrenia (n=26) were compared with patients with personality disorders and neurosis (n=27), neurotic depression (n=9) and psychotic depression (n=3), items included those used by Hertzig and Birch (62;63) (cranial nerves, stereognosis, graphesthesia, reflexes, coordination, sensation, movement disorders, speech, activity, developmental abnormalities, extinction, motor impersistence, auditory-visual integration, and adventitious motor overflow). They found that schizophrenia patients have more SNS compared with the other groups. However affective disorder patients did not have more SNS compared with controls. Interestingly the personality disorder/neurosis group was found to have increased SNS similar to the schizophrenia group

Cox (45) compared SNS in schizophrenia, alcohol dependence syndrome, unipolar disorder, bipolar disorder, mixed personality disorder, anxiety disorders and healthy controls. They grouped SNS according to the putative cortical areas of involvement

into frontal, parietal, temporal and occipital subsets. Schizophrenic patients were significantly more impaired compared to all other diagnostic groups in relation to frontal signs. For parietal signs, unipolar depressive patients were as impaired as schizophrenia patients, both groups being more impaired than other groups. The authors concluded that the specific increase in frontal signs and the relatively specific increase in parietal signs in schizophrenia may be related to attention impairment in schizophrenia. The authors also highlighted the lack of difference between most other diagnostic groups and controls although this conclusion is weakened by the relatively modest sample sizes (n=10-20). This study was also characterized by the inclusion of a number of cognitive assessments (particularly in the frontal and temporal subscales). Some of these were not often included in other SNS definitions.

Walker (60) compared "neuromotor" functions (stereognosis, mirror movements, L/R orientation, oculomotor function, muscle tone, movement regularity) between patients with schizophrenia, schizoaffective disorder and affective disorder (15 in each group). She also found that greater abnormality was found in the schizophrenia group (differences reached significance for stereognosis, Left Right orientation, and oculomotor functions).

Nasrallah (64) studied 44 schizophrenia patients, 28 mania patients , and 29 controls. He found that SNS in manic and schizophrenic patients were both increased relative to controls. SNS level in mania was not significantly different from schizophrenic patients. Gureje (65) reported that in Nigerian patients, most signs were found in

similar levels between schizophrenic and affective disorder patients. When compared with controls, only left-right disorientation distinguishes schizophrenic patients from controls. The findings in this study are different from most other studies in that high prevalence of SNS were also present in the control group. This raised the potential question of ethnic variation in SNS. The author also pondered the possibility that there might be an association with obstetric complications. Krebs (54) also found that SNS score was higher in schizophrenia than in affective disorder patients (48;66). In a further review of the specificity of neurological signs in schizophrenia, Boks (67) reviewed 17 studies and evaluated the weighted mean prevalence of 30 neurological signs. The authors concluded that most signs were equally present in mood disorder and in schizophrenia. However, several signs were more prevalent in affective disorder (stereoagnosia and rhythm tapping). Other signs are more prevalent in schizophrenia compared with mood disorder (extinction, dysdiadochokinesis, tandem, finger thumb opposition, articulation) and thus appear more specific for schizophrenia, the specificity of "motor sequencing" signs are unclear.

Comparison studies are needed to assess different diagnostic populations with the same methodology. In addition the stage of illness when the patient is under investigation may also affect the result. For instance it is possible that in addition to being a trait marker, SNS may also increase during an episode of psychosis or mood disturbance. It is important that comparison be carried out in comparable stages, preferably in remission from episodic disturbance.

Currently, it is still unclear whether there is an increase in overall SNS in schizophrenia relative to affective disorder. The meta-analysis results of Bok (67) suggested an interesting possibility that certain SNS may be specifically increased in schizophrenia while some others are more specific for affective disorder. Few studies have directly addressed this issue on an item-to-item basis. This is an important area requiring further study. In addition to the possible inherent heterogeneity amongst SNS, some of the variation may be related to the boundaries of mood disorders, as there is considerable heterogeneity within mood disorder itself.

SNS in schizophrenia and other psychiatric disorders

In the reviewed by Heinrich and Buchanan (46), SNS was found to be higher in schizophrenia compared with patients with personality disorder, neurosis and substance abuse in a number of studies (41;45;56;58;62;63;68;69). In addition, Almeida (70) found that SNS (finger-thumb opposition, dysdiadochokinesia, fist edge palm, foot taps, agraphesthesia) was increased in late paraphrenia compared with controls. Patients with SNS also had more cognitive impairment and negative symptoms (71).

Predictive specificity

There is little available data directly addressing the predictive specificity of SNS for schizophrenia. The presence of SNS in high-risk subjects will be discussed in a following section. In terms of specific predictive value of childhood SNS, Shaffer (38) compared adolescents known to have SNS at age 7 and those that did not have

SNS at that age, and found that the former group had lower IQ and more depression, withdrawal, and anxiety. There was no relationship with attention deficit or conduct disorders. Importantly most of the variance was accounted for by SNS independently of IQ. This study has sometimes been interpreted as indicating a relationship between soft signs and future affective disorder rather than schizophrenia. It is important to note that the identified conditions of depression, withdrawal and anxiety are more prevalent than schizophrenia in the age range studied. In addition the follow-up age of 17 years was largely before the peak onset age for schizophrenia. Since some of these symptoms are known to be present in prodromal stages of schizophrenia, the possibility that some of the individuals may later develop schizophrenia cannot be ruled out.

Aetiology

Twin studies

Amongst MZ twins discordant for schizophrenia, SNS was found in both twins, but were more pronounced in the affected twin compared with the well twin (72-74). The level of SNS in the well co-twin lies in between the ill co-twin and the normal population (75). Taken together the evidence suggests that both genetic and environmental factors are important in determining the level of SNS.

Cantor-Craae (73) further found that the extent of SNS in the well discordant co-twin was related to a history of neonatal complication, while a history of substance abuse and postnatal cerebral trauma were not related to SNS level. The authors concluded

that peri-natal complication might contribute towards SNS manifestation.

Family studies

Several reports have found that first degree relatives of schizophrenic patients have more neurological abnormality including SNS (46;50;76).

Rossi et al (50) using a 26-item SNS battery based on Quitkins (42), studied 58 DSM-III schizophrenic patients, 31 first degree relatives and 38 normal control (mean age 34.8 education level 8 years). They found that SNS prevalence amongst first degree relative was similar to schizophrenic patients, while both groups had increased SNS compared with normal control. Likewise Chen et al (77), in a sibling study involving 15 patient and their siblings using the CNI, found that there was a differential pattern in subgroups of signs. Disinhibition signs were similar between sibling and patients groups. Motor coordination signs of sibling were at a level between patients and control. Sensory integration signs were similar between sibling and control subjects. This finding suggests possible heterogeneity amongst SNS in the extent of genetic contributions.

High-risk studies

In line with family studies, increased SNS have been found in studies of high-risk groups (40;78;79). Lawrie (80) in the Edinburgh high-risk study found that SNS was more frequent in 152 medication-free high-risk subjects whether with or without psychotic symptoms. There are as yet few studies on general populations with

measures of "psychosis proneness" or schizotypal personality traits. Obiols et al (81) studied adolescence with poor CPT performance in (motor coordination, motor overflow, sensory signs, asymmetry) but found no association between SNS and CPT performance.

Perinatal complications

SNS was found to be increased in children with perinatal obstetric complications (82). It is suggested that obstetric complications are related to SNS expression (83). Schizophrenic patients with a history of perinatal complications appear to have particularly more neurological aberrations and cognitive deficits (9;84).

Demographic correlates

Age

The relationship between age and SNS is inconsistent across studies. Several studies did not found a relationship between age and SNS (74;85) while some studies reported a correlation (68;86). In Merrian (87), 28 chronic schizophrenic patients were assessed with a scale including apraxia, fine motor function, prefrontal, parietal and non-localizing signs. No association with age was found. However, Cuesta (88;89) studied frontal signs (FS) and neuropsychological performance and found that FS was related to age. Different inclusion age range amongst studies was considered as a potential contributor to the inconsistency. One important limitation in a cross-sectional study is that age is confounded by illness duration, which might itself have an impact on SNS.

Gender difference

Prevalence of SNS

More SNS impairments in males were reported in a few earlier studies (41;61). However, in most studies of SNS, no gender difference in the overall level of soft neurological signs was identified (53;62;63;84;85;89-92). However an interesting observation emerged from the studies looking at SNS correlates. Malla (53) found that there was a gender difference in the clinical correlates of SNS factors. Different SNS factors were related to Psychomotor poverty in male and female patients.

Intelligence and education level

The relationship between lower intelligence level and SNS amongst schizophrenic patients has been reported in a number of studies (74;88;89;91). Notably, the relationship was not only observed in chronic patients with more severe disabilities, but also in younger patients, with good functioning levels and early in the course of the illness (91).

The correlation between SNS and intelligence level was found not only in schizophrenia, but also in personality disorder and affective disorder patients (42); normal children, learning disabled children (93), as well as in high-risk children (with family history of schizophrenia) (94).

A smaller number of studies did not find this relationship (87;95;96). Two notable exceptions to the findings were Merrian (87), who in 28 chronic schizophrenic

patients did not find associations between with SNS and IQ. The conclusions are limited by the small sample size. However Flashman et al (95) divided 176 schizophrenic patients into those with (n=68) or without (n=108) SNS and compared neuropsychological performance between the two groups. He found no difference in WAIS-R Verbal and performance IQ between the two groups.

A further study compared people with co-morbidity of schizophrenia and learning difficulties (IQ 50-70 range, mean age 48.6) (n=39) (97), with matched (age and gender) control groups either (1) mild learning disability without schizophrenia (n=28); or (2) schizophrenia without learning disability (n=34). Subjects were assessed using the NART, the Quick IQ test, the Rivermead Behavioural Memory Test as well as SNS assessment with the NES. Mean IQ scores between learning disabled subjects with or without schizophrenia did not differ. The co-morbid group and the learning disability group both showed increased SNS compared with the schizophrenic group. There was no correlation between SNS and intelligence score in any of the groups. The study also found a tendency for co-morbid subjects to belong to multiple affected families and raised different possible mechanisms in which schizophrenia might be associated with intelligence impairment.

Ethnicity

Buchanan and Heinrich (31) reported that healthy African Americans have an increased level of soft signs compared with Caucasians. The increase was particularly found in the sensory integration subscale. Gureje (65) also found

increased prevalence of SNS among Nigerian patients as well as control subjects and speculated that it might relate to the level of obstetric care. There is no systematic data on SNS for other ethnic groups.

Premorbid functioning

The presence of SNS was found to be related to poor premorbid adjustments in Gupta (49). Quitkin (42) also reported increased SNS in schizophrenic patients with poor premorbid functioning. This association was however not found in some other studies (68;85).

Clinical correlates

A number of studies have addressed SNS in relation to clinical symptom dimensions. Commonly there are two approaches. In the first approach patients are classified into subgroups and then SNS are compared between the subgroups. In the second approach the statistical relationship between SNS and symptoms dimensions are considered in the same population of patients.

Comparison of SNS between schizophrenia subtypes

A relatively small number of studies followed this approach. Nasrallah (98) compared paranoid (n=20) and non-paranoid (n=24) schizophrenic patients (according to the Tsuang-Winokur criteria) with respect to 19 soft neurological signs and found no difference between the groups. Gureje (65) also found that SNS did not differ between paranoid and non-paranoid schizophrenia. Galderisi (99) found that

SNS was increased in simple schizophrenia compared to other subtypes.

Relationship with symptom dimensions

Negative symptoms

A substantial number of studies reported correlation between SNS and negative symptoms (41;47;53;87;91;100-102). Some of these are further described below. In the study of Malla (53), NES scores were correlated with negative symptom scores. In Liddle's (103) study involving a group of 47 chronic schizophrenic patients, SNS were correlated with the psychomotor poverty syndrome (r=0.34) and the disorganization syndrome but not with reality distortion syndrome scores. Within the psychomotor poverty syndrome, decreased spontaneous movement and poverty of speech were particularly correlated with SNS scores. A subsequent study also identified that the signs of dyspraxia and agnosia associated most strongly with negative symptoms (104). In Merrian (87), "Prefrontal" signs were associated with negative symptoms, positive symptoms were associated with parietal and non-localizing signs. King (105) studied 16 chronic schizophrenic patients; SNS were correlated with both positive and negative symptoms. In Wong (100), 37 patients with chronic schizophrenia (18-65, DSM III R) were assessed using Convits Quantified neurologic scale (covering frontal, SNS and cerebellar signs). SNS and frontal signs were both found to be correlated with negative symptoms. Smith (106) also found that neurological signs correlated with negative symptoms. In Cuesta (89) frontal signs were found to be related to SANS scores but not SAPS scores. Likewise, in Mohr (91), both negative symptoms and positive symptoms correlated with SNS

scores. In Arango (107), deficit syndrome was related only to sensory integration signs. Only a small number of studies yielded negative findings (e.g. Kolakowska et al (85) found that SNS was not related to negative symptoms). Thus, the relationship between negative symptoms and SNS appears to be a robust observation found in most studies.

Formal Thought Disorder and disorganization

In an early study of Tucker (68), 109 patients with mixed diagnoses were classified as being schizophrenic (n=38) and non-schizophrenic (New-Haven Schizophrenia index and Schneider First Rank Symptoms Scale), thought disorder was scored with the Goldstein-Scheerer Object Sorting test, targeting overinclusive, idiosyncratic, and underinclusive thinking. SNS (including finger agnosia, finger tip writing, tactile form recognition and the Halstead Tactual Performance test) were found to be related to both a diagnosis of schizophrenia and the presence of thought disorder. In a subsequent study, SNS, along with other motor dysfunction, was also found to be related to thought disorder (47). In Liddle 1987's (103) study involving a group of 47 chronic schizophrenic patients, SNS were correlated with disorganization syndrome scores (r=0.37). Amongst other signs, dyspraxia and agnosia were particularly associated with the disorganization syndrome (104). Schroder (108) also found that SNS was increased in patients with disorganization symptoms (n=50, mean age =32, using the Heidelberg scale). In the study of Arango (107), disorganization was related to total NES score but not the subscale scores. However, in Malla's (53) data (NES in n=100 age= 33, illness duration 3 years), no relationship between SNS and

disorganization was found. The overall picture remains conflicting, though there is suggestive evidence for the association between SNS and thought disorder.

Positive symptoms

Generally studies have not identified a robust relationship between SNS and positive symptoms. Kolakowska (85) found that SNS were not related to positive symptoms. In Liddle 1987's (103) study described above, SNS while correlated with disorganization syndrome and psychomotor poverty (negative) syndrome, were not correlated with reality distortion (positive) syndrome scores. Cuesta (89) also found that frontal signs related to SANS but not to SAPS scores. In the Arango (107) study involving 83 patients positive symptoms were not related to SNS. Likewise in Wong (100), neither SNS nor frontal signs was correlated with positive symptoms scores.

However, Merrian (87) reported that while prefrontal signs were associated with negative symptoms, positive symptoms were associated with parietal and non-localizing signs. King (105) studied 16 chronic schizophrenic patients and found that SNS were correlated with both positive and negative symptoms. Likewise, Mohr (91) also found that both negative symptoms and positive symptoms correlated with SNS scores.

One difficulty in clarifying the relationship with positive symptoms is that in cross-sectional studies, it is often not clear whether positive symptoms are related to relapse or represent residual symptoms. These two situations may have different

significance in terms of relationship with underlying features.

Age of onset

The relationship between SNS and age of onset is also contentious, SNS was found to be related to earlier age of onset in some studies (46;52;58) but this finding has not been replicated in other studies (69;85;89). It is important to note that while age of onset, current age, and illness duration might each be linked to SNS through different mechanisms, they are at the same time confounding one another.

Course and outcome

SNS has been found to be increased in medication-naïve first-episode schizophrenic patients (52;109;110). When Flyckt et al (111) compared hard signs and psychomotor tests and found no significant difference between first episode and chronic patients, they concluded that the level of SNS identified at first episode appears to be stable with time. This conclusion is limited by the power of the study and the difference in sampling between the acute and the chronic patient samples. Generally speaking, a subset of first episode patients (particularly those who do well) are less likely to be in contact with the service over a long period of time, and patients who do less well are more likely to be recruited into a cross-sectional study. If SNS is related to illness severity, this would tend to bias the study in favor of finding increased SNS in more chronic patients. Therefore, the finding of similar level of SNS between first episode patients compared with chronic patients would even suggest possibly a degree of improvement in SNS for some patients after the first episode.

Illness chronicity

Whether SNS progresses with longer illness duration is an important question. If SNS are stable with time it would suggest that they reflect features largely determined at the developmental stages. On the other hand if SNS increases with the course of illness, it would suggest that SNS might express features that are vulnerable to deterioration. Data addressing the relationship between SNS and illness duration is conflicting. In Kolakowska's study (112), subjects with SNS were found to have longer illness duration than those without, however when stratified into smaller groups according to illness duration, the proportion of those with SNS was not significantly different. In Flashman et al (95), patients with more SNS had a longer illness duration (i.e. they had a younger age of onset when compared with a comparison group with the same current age). Cuesta et al. (88;89) also found that frontal signs were related to duration of illness. Others have failed to find a relationship (91;113). Flyckt et al (111) compared motor tests (including SNS) between first episode psychotic patients and chronic patients and found no significant difference.

Outcome

Johnstone et al (114) found that neurological signs were associated with worse outcome in 253 first-episode schizophrenia patients (in terms of staying for more than100 days in hospital in first 2 years). In Wong et al (100), SNS and frontal signs were each found to be correlated with GAF, social performance and PANSS negative symptoms. Kolakowska et al (112) however found that SNS was not related to

overall clinical outcome. SNS was also not related to re-hospitalizations at 3 years (92).

Medication

Comparison studies between medicated patients and medication-free patients generally revealed no difference in SNS (45;47;56;57;59;60). Flyckt (111) compared hard signs and psychomotor tests performances between medicated and medication free patients (relatively small sample) and found no difference between the groups. Most studies also found no relationship with duration on medication and cumulative dosage of medication (74;88;111;112). Notably NES scores remained stable despite a change from conventional antipsychotics to clozapine medication (115). In terms of side effects, King (105)studied 16 chronic schizophrenic patients (average illness duration of 21 years) on 10 SNS and found that SNS were correlated with tardive dyskinesia. In addition, Motor coordination score in NES was also found to be correlated with extrapyramidal signs (115).

Relationship to cognitive function

Impaired cognitive performance in schizophrenia has been extensively studied and documented. A full account is beyond the scope of the current dissertation. Briefly, it is likely that there is a "generalized" cognitive impairment in schizophrenic patients (116). It is more contentious whether additional specific impairments can be identified. The current view is that specific impairments probably do exist but there is considerable heterogeneity. They include variable profile of impairments in

attention, memory, language, as well as executive functions.

Existing evidence suggest that like SNS, subtle intellectual impairments may be present many years before the onset of overt psychosis. Significant neuropsychological impairment is already present at the first presentation of illness (117) though there has been some debate over whether cognitive impairment subsequently runs a deteriorating course. Such a progressive course would suggest a degenerative process, whereas an absence of progression would suggest a static process that occurs around (or prior to) the onset of the psychosis, but remains stable thereafter.

Progression in cognitive impairment in schizophrenia have been systematically studied over the last few decades (118;119). Some of the earlier studies were conducted before standardized diagnostic criteria were widely used. There have been few recent longitudinal studies and those conducted tend to suffer from small sample sizes, high drop-out rates and relatively short follow-up periods. Waddington et al (120) followed 51 relatively older patients for five years (mean age 57 years) and found no overall decline on a 10-item global cognitive rating. Goldstein and Zubin (121) compared younger and older schizophrenic patients on their performance in the Halstead-Reiten Battery and found no significant difference in rate of cognitive decline compared with those of controls. Among cross-sectional studies, Heaton et al (122) compared neuropsychological deficits in 85 younger, and 35 older early-onset patients, as well as 22 late-onset patients and concluded that deficits were no more

marked in patients with longer duration of illness. However, Bilder et al (117) compared 33 first-episode schizophrenic patients with 34 chronic patients and reported evidence for progression in cognitive deficit. In a cross-sectional study comparing 74 patients in different age ranges, Goldberg et al (123) and Hyde et al (124) reported no evidence of cognitive decline using an extensive neuropsychological battery. Prefrontal dysfunction has been postulated to be pivotal to the cognitive difficulties manifested in schizophrenia. Schizophrenic patients have been found to perform poorly on prefrontal function tasks (such as the Wisconsin Card Sorting Test and semantic fluency). Whether the prefrontal dysfunction is progressive is contentious. Set off against the negative findings of Hyde et al (124) described above, Sweeney et al (125) compared 27 first episode patients with 33 chronic patients and described poorer semantic fluency and Wisconsin Card Sorting Test performance in the chronic patients. Unfortunately in this study there was no attempt to control for the effect of age and it is difficult to ascertain to what extent the poorer performance was related to aging *per se*.

Theoretical considerations

In considering the relationship between cognitive function and SNS, it is important to examine the underlying assumption about explanatory levels. One position is to consider cognitive function as phenomena at a more "basic" level of explanation and to attempt to explain certain neurological signs in terms of these more basic cognitive processes. While this may make some sense for particular cases, in general the assumption cannot be uncritically justified. Indeed from the consideration of the

boundary between cognitive paradigms and neurological signs in Chapter 1, as well as from the design of some of the existing studies, it is clear that it is also possible to consider both cognitive function and SNS as phenomena occurring at the same explanatory level. That is to say, they are both driven by more basic processes not captured in either approach. In this situation it would not make sense to attempt to explain one domain in terms of another. Instead, it would be more prudent to examine the relationship between the two domains without prior assumption about directions of causality. This is the approach that is taken in the current analysis.

Empirical relationship between SNS and cognitive function

Although there have been few systematic studies of the relationship between neurological signs and cognitive functions, a limited number of studies have reported, among other findings, global correlation between neurological signs and neuropsychological impairment in the same sample of schizophrenic patients. Owens and Johnstone (101) found that there was a modest correlation between cognitive performance and neurological signs (mostly extrapyramidal signs) in 510 schizophrenic inpatients. However, in a further study involving 120 patients discharged from hospital, the research group did not find significant correlation between neurological abnormality and cognitive performance (126). In contrast, in a small sample of 16 patients, King et al. (105) reported a strong correlation between neurological signs and cognitive ability (Spearman coefficient -0.818, $p<0.01$). Likewise, in another study involving 37 patients, total score in neurological signs was also found to be correlated with a global score in cognitive function (85). Liddle

(103) further observed that in 47 patients, total neurological signs score was correlated with scores in a variety of cognitive tests. With a slightly different design, Merrian et al (87) divided neurological signs into five areas (prefrontal, parietal, praxis, fine motor coordination, and non-localizing) and applied a vocabulary test and a visual reproduction test to the patients. They studied 28 patients and concluded that they could not detect correlation between neurological signs and cognitive performance.

Taken together, while these earlier studies suggest a potential relationship between neurological signs and neuropsychological impairment, the exact relationship remains unclear. Most of these studies employed a relatively small number of subjects. Often a single measure was derived from either neurological signs or cognitive performance, thus potentially masking more specific relationship between smaller unit of analysis within these two domains. In addition, few of the studies considered the potential confounding effects of age and education level.

Several more recent studies began to address the relationship in more detail. Mohr (91) reported that in 93 patients all NES subscale scores were correlated with standard progressive Raven matrices (as a measure of intelligence) and with WCST perseveration. The correlation with WCST performance remained significant after partialing out Progressive Raven matrices scores, thus suggesting a specific relationship with executive function independent of general intelligence. Cuesta (89) studied FS and neuropsychological performance and also reported a specific pattern

of relationship. Importantly they also used partial correlation to account for effects of age, education level and illness duration. A specific profile of correlation between frontal signs and various neuropsychological tests emerged. FS was found to be related to WAIS similarity, digit span, vocabulary, block design, Rey complex figure and, Trail-making, but neither with visual memory nor verbal fluency. In another approach, Flashman (95) divided schizophrenic patients (n=176) into those with (n=68) or without (n=108) SNS and compare neuropsychology performance between the 2 groups. It was found that those with SNS performed worse in cognitive tests that required motor speed and coordination (finger tapping, Purdue Pegboard, Trail B, Rey Osterreith complex figure copy) even after partialing out extrapyramidal signs and dyskinesia scores. However the groups did not differ in a range of other tasks (verbal memory, Ray complex figure memory, Benton visual retention WCST categories or perseverative errors, Stroop, verbal fluency, continuous performance tests, as well as WAIS-R Verbal and performance scores). The authors suggested that the relationship between SNS and cognitive functions was circumscribed rather than general. In the study of Wong described above (100), Convits Quantified neurologic scale scores were associated with impairment on the visual illusion and span of apprehension tasks. Backward masking impairments were associated with SNS alone (not frontal tasks). Arango et al (127) attempted to explore whether NES (as well as frontal release signs, eye movement, short term memory) scores predict neuropsychological performance (Trailmaking, fluency, WMS, Stroop, Mooney faces, WAIS-R block design, CPT, Span of apprehension, MMSE, WAIS-R verbal and

performance). Their results indicated that "sensory integration" score was the most frequent predictor of neuropsychological test performance. It predicted the performance in fluency, trailmaking, Block design, logical memory, visual reproduction, visual pairs, MMSE, as well as WAIS-R verbal and performance scales. "Motor coordination" jointly predicted "visual pairs" performance. "Complex sequencing" predicted Stroop test and figural memory subscale scores. The authors pointed out that neurological signs did not explain most of the variances of neuropsychological performance and suggest that SNS and neuropsychological performance each capture unique variances.

Although some of these studies did not employ a sufficient sample size in view of the large number of variables investigated, the overall relationship between global cognitive function and SNS seems to be supported by several studies. However, the extent to which this relationship is influenced by the known relationship between SNS and intelligence has not been clarified. This issue necessitates a consideration of the complex relationship between intelligence and cognitive function performance. Several studies have also suggested relationship between specific domains of SNS and domains of cognitive function. This relationship requires further clarification.

3 Core methodology

Introduction

In this chapter a description of the assessment procedures common to the set of studies that constitute the dissertation will be provided. These studies were carried out at two locations (Hong Kong and UK) spanning a period of ten years, and involved a number of sites and collaborators (details in Appendix I). The themes that thread the studies together are the investigation of the characteristics of soft neurological signs in schizophrenic patients, using a similar set of instruments. The investigations started with cross-sectional studies in order to identify demographic, clinical and cognitive correlates of SNS. These were followed by two longitudinal studies to address the changes in level of SNS over time in different stages of schizophrenia. One of the longitudinal studies addressed stable patients with long illness duration; the other study addressed first episode psychosis patients. Consistency and coherence within this set of studies lies in the fact that similar instruments and definitions have been employed across these studies. Despite the uniformity in methodology, each study was conceived with independent research questions at the time and each was exposed to unique sets of practical constraints. These will be described more fully in subsequent Chapters.

Some minor variations have emerged over time (e.g. in the item inclusion in subscales). Consequently, in order to extract more comparable information across the

studies, it has been necessary to review the definition of SNS subgroups and subgroup scores, so that a standardized set of criteria is used. This has necessitated a fresh analysis of raw data from the studies. The set of studies will be briefly described below. This is followed by a description of the evaluation instruments used in the studies.

Overview of studies

For the sake of clarity numbering is assigned to the studies. All the studies has approval from the relevant research ethics committees. Unless otherwise specified the studies were carried out in Hong Kong and involved ethnic Chinese subjects.

Study 1

The study focused on a large clinical sample of schizophrenic patients at various stages of their illness. In this study the primary objective was to explore relationship between soft neurological signs and other demographic, clinical and cognitive features of the disorder (Chapters 5 and 6). A local normative sample was also evaluated.

Study 2

This cross-sectional study included Caucasian subjects from the UK. There was a normative sample and a clinical sample of chronic schizophrenic patients. As reliability was monitored across study 1 and study 2, it was possible to carry out a

cross-ethnic comparison between healthy control subjects in the two studies. Data from this study was used only for the purpose of cross-ethnic comparison in this dissertation (Chapter 5). Extensive clinical information was not available for this sample.

Study 3

This study aimed at 3-year longitudinal follow-up data in a group of stable chronic inpatients. The sample had relatively long illness duration and was also approaching the fifth decades in age (Chapter 7). The key issue addressed was whether there was a progression in SNS over the 3-year follow-up period independent of any clinical changes.

Study 4

In this study motor soft neurological signs were studied in first episode patients with followed-up at regular intervals for a period of two years. This was part of a larger study involving longitudinal follow-up of patients with first episode psychosis. The key questions addressed were whether the level of SNS in medication-naïve patients was increased, and whether there was longitudinal change in SNS in the 2 years after treatment of the first episode (Chapter 8). This study also provided the opportunity to investigate correlates of SNS in a first episode sample.

Assessment Tools and procedures

Assessment of SNS

The Cambridge Neurological Inventory (CNI)

In the construction of this assessment instrument for soft neurological signs it was emphasized that items in the inventory should be operationalized to reduce variations in elicitation and scoring, and that items contained in SNS subscales should also be explicitly listed so that comparison across studies could be facilitated.

A literature review was carried out to identify all CNS signs of potential significance in psychiatric disorders. Items were taken from established descriptions and scales of SNS (18;31;42;60;87;128;129) (also see Appendix 4). For neurological signs not covered by these established instruments, descriptions from primary source were traced and operationalization constructed (e.g. utilization behavior). In addition an abbreviated standard neurological examination was incorporated after consultation with a neurologist (JRH). Where different descriptions existed preference was given to 1) more detailed and explicit operationalization in elicitation and rating; and 2) more widespread use in previous research. Some previous batteries have included cognitive tests. Such direct tests of higher cognitive function (e.g. language, memory, spatial performance) were not included in the CNI, and so were tests requiring extensive use of specific equipments (such as reaction time tests).

After initial piloting, signs that were difficult to administer or rate were excluded (e.g. blink rate and utilization behaviour). A revised version of the inventory was then

constructed. A full description of the CNI examination procedure, as well as the elicitation and scoring of each of the signs, is included in appendix 2. To ensure consistency, apart from textual description, an instructional videotape was made demonstrating the elicitation of each of the signs. The candidate personally trained all raters involved in the studies.

The CNI offered instructions for eliciting and rating a comprehensive range of neurological signs in 7 domains. Three of these CNI subscales addressed SNS (motor coordination, sensory integration, disinhibition) and they are included in the main analysis of the present study. Items included in these subscales are shown in Table 3.1. The motor coordination subscale consisted of SNS that involved regularly paced repetitive positioning involving the upper limb. These signs ranged from the simple finger tapping to the more complex fist-edge-palm test. The sensory integration SNS involved higher cognitive processing of perceptual information from different sensory modalities. The disinhibition subscale included SNS that elicit spurious responses that are irregular either in time (e.g. go-nogo) or in space (e.g. mirror movements).

In the original ratings scale, scoring was made according to standardized anchor points to indicate "normal" response (0), "equivocal" response (0.5), "abnormal" response (1) or "grossly abnormal" response (2). In data analysis throughout this dissertation, items scores were further collapsed into either "absent" (covering "normal" or "equivocal" scale scores) or "present" (covering "abnormal" or "grossly

abnormal" scale scores). For items that can be scored on both left and right, each is treated as an independent score. To facilitate comparison between different subscales, a scaled score is defined as the summed items score divided by the possible score range for the subscale, and then converted to a 0-to-100 scale (i.e. percent score). In the studies reported, it was not possible to make the raters of neurological signs blind to the group of the subjects (i.e. patients or healthy controls).

Table 3.1. SNS subscale items in the CNI

Motor coordination
Finger-thumb opposition (Left and Right)
Finger-thumb tapping (Left and Right)
Dysdiadochokinesia (Left and Right)
Fist-edge-palm test (Left and Right)
Ozereski test
Sensory integration
Extinction
Finger agnosia (Left and Right)
Stereoagnosia (Left and Right)
Graphaesthesia (Left and Right)
Left-right disorientation
Disinhibition
Saccade blink
Saccade head movement
Unilateral winking
Mirror movements 1,2 (Left and Right)
Go-no go sign

Reliability

The following raters were involved in the studies

1 CK (Studies 1,3,4)
2 LL (Study 1)
3 DN (Study 1)
4 EC (Studies 1,2,3,4)
5 RC (Study 1)
6 JS (Study 2)

Interrater reliability on the subscale scores was calculated for each of the subscales based on investigators' ratings on the same set of 15 videotaped CNI examinations. The interrater reliability scores were calculated based on pooled data from the 6 investigators involved in the UK and the HK studies. Overall intraclass correlation for the soft neurological signs subscales ranged from 0.88 to 0.94. (Table 3.2)

Table 3.2. Intraclass correlations for CNI total and SNS subscales scores

	F-value	df	p-value	ICC
Motor Coordination	13.37	82, 656	<0.0005	0.93
Sensory integration	4.46	70, 490	<0.0005	0.78
Disinhibition	2.71	80, 560	<0.0005	0.68
Total CNI score	6.07	69, 6348	<0.0005	0.84

ICC Intraclass correlation coefficient

Assessment of clinical picture

Schizophrenic symptoms

In studies 1 and 3, symptom assessments were carried out with the 18-item Brief Psychiatric Rating Scale (BPRS) (130), which has been successfully applied to Hong Kong Chinese patients (131). Interrater reliability of the BPRS items for the

investigators ranged from 0.84 to 0.99 (intraclass correlation). In study 4, symptoms were assessed using the PANSS. The reliability for the PANSS in study 4 was separately assessed. The overall intraclass correlation coefficient for the PANSS was 0.83 (0.83 for the positive subscale, 0.73 for the negative subscale). These symptoms rating scales were scored according to standardized instructions based on clinical interview and medical records.

Negative symptoms

Negative symptoms were in addition assessed using the High Royds Evaluation of Negativity (HEN) (93). The HEN consisted of subscales in the domains of appearance, behaviour, speech, thought, affect, functioning as well as a global score. Validation of the HEN for use in Hong Kong Chinese patients has been previously reported (132). The interrater reliability for global score in the HEN was 0.92. The intraclass correlation for the subscales ranged from 0.74 (thought) to 0.85 (speech).

Medication

For studies 1 to 3, all patients were on conventional antipsychotics. Dosages were converted to chlorpromazine equivalence according to Davis (133). The dosage of anticholingeric medication (Benzhexol) was also recorded. Atypical antipsychotics (risperidone and olanzepine) were only involved in study 4 and the number of patients on atypical anitpsychotics was noted.

Side-effects rating scales

In studies 1 to 3, extrapyramidal signs and dyskinesia were assessed with build-in subscales in the CNI. In study 4, extrapyramidal signs were assessed with the Simpson Angus scale (134), dyskinesia was assessed with the Abnormal Involuntary Movements Scale (AIMS) (135), akasthisia was assessed with the Barnes scale (136).

Assessment of cognitive performance

Cognitive function tests were selected based on the following criteria

- Addressing cognitive function domains of interest in schizophrenia (attention, memory, executive functions)
- Acceptability and portability
- Tests widely employed in other studies
- Previous use by the candidate and his research collaborators

Tests were carried out in a fixed order with flexible rest periods provided as needed. They are described in the following sections.

Semantic fluency

Semantic fluency was assessed by requesting the patient to name as many exemplars as possible from each of three categories ('food', 'animal', and 'furniture') in one minute. In study 3 and 4, only one category (animals) was assessed. The responses

were tape recorded and later transcribed for analysis. A total score was computed by counting the number of correct items produced in one minute (repeated items and items clearly outside the category were not counted).

Wisconsin Card Sorting Test

In studies 1 to 3, the Wisconsin Card Sorting Test was performed and scored according to standard procedures (137). In the WCST, subjects were presented with cards in which design elements were printed in different colors, numbers and shapes. Four cards were laid on the table and the subjects were given additional cards one by one. Subjects were instructed to relate the additional card to one of the four cards on the table according to a rule that the examiner was aware of but the subject was not. Subjects were told only whether the sorting was correct or not. A next card was then presented for the next round of sorting. The sorting rule could be according to color, shape, or number. After 10 consecutive correct responses, the sorting rule changed. Sortings according to previously correct but currently incorrect rule are considered perseverative errors. Perseverative errors were scored as defined in Heaton (137).

The modified Wisconsin Card Sorting test

The modified Wisconsin Card Sorting test was adopted in study 4. The procedures describe by Nelson (138) was followed. Briefly, in the modified version, only 64 cards were used. The modified version also excluded conditions where two possible rules were simultaneously compatible with a given feedback. Subjects were also

alerted to a change of rule when it occurs.

WAIS-R subscales

Digit Span (forward and backward), Comprehension, Similarity and Information subtests from the Wechsler Adult Intelligence Scale WAIS-R-HK (139) (Revised Cantonese Version, Hong Kong Psychological Society, 1989) were carried out and rated according to standard procedures. *Digit Span* assessed the ability to hold a limited number of digits for several seconds. Digits were presented at a rate of one item per second in order to avoid chunking effect. Sequences started from 3 digits and following successful attempts, successively longer sequences were presented until the subject was unable to correctly recall the sequence. The length of the longest sequence successfully recalled was the *forward digit span. Backward digit span* was tested in a similar fashion with the additional requirement that the subject had to recall the digits in a reversed order. Both *forward* and *backward digit spans* were used to calculate verbal intelligences according to standardized procedures. In the *information* subscale, subjects were asked a range of questions on common knowledge items. In the *similarity* subscale, subjects were asked to describe the similarity between pairs of objects. Their responses were recorded and scored according to standard procedure. In the *comprehension* subscales, subjects were presented with everyday scenarios in which they were asked how they would have responded. Again, responses were recorded and scored in a standardized manner.

Memory tests

Logical Memory and Visual Reproduction were performed as described in the Wechsler Memory Scale Revised (139) (adapted for Cantonese speaking patients, C.W. Wong, personal communication). In the Logical Memory test, subjects were presented with short narratives. They were instructed to listen to the narrative and to recall it immediately afterwards (immediate recall) as well as 30 minutes later (delayed recall). The number of units of information that were successfully recalled was scored. It was found that immediate recall and delayed recall performance were highly correlated. Unless otherwise specified, immediate recall performance data was presented. The Visual Reproduction subscale of the WMS involved memorizing abstract line figures, subjects were instructed to reproduce the figures after the they were withdrawn from sight (immediate recall) and 30 minutes later (delayed recall). Once again, the immediate and delayed recall performances were highly correlated and only immediate recall data were presented in the data analysis.

The tone counting task

Sustained attention was assessed by the tone counting task (adapted from (140)). Subjects were asked to silently count the number of tones embedded in each of the 12 trains of brief pure tones (360 Hz frequency, 250 msec duration) presented at a regular pace of one per second. The tones were delivered by a loudspeaker adjusted to a comfortable level of loudness for the patient. For each of the 12 trials, the number of tones varied between 1 and 12 in a randomized order. After each train of

stimuli, subjects were asked to immediately report the number of tones counted. Accuracy was scored as the number of correct counts out of the 12 trials (maximum 12, minimum 0). This simple test of attention has been validated neuropsychologically (140). Application of this test as a measure of sustained attention in schizophrenia has been reported elsewhere (132).

Premorbid intelligence estimation

For Chinese subjects, verbal IQ estimates was derived from the information subscale of the WAIS-R-HK (139). The information subscale was selected as data from a previous pilot study indicated that amongst other subscales it correlated most strongly with the prorated verbal IQ score obtained from using a larger number of subscales (Digit span, comprehension, similarities, information). Unfortunately at the time of the study, the validity of the vocabulary subscale for use in the Hong Kong population was yet to be established. Attempts to construct a local equivalent measure to NART have not yet been achieved, largely due to the prevalence of bilingualism amongst Hong Kong Chinese subjects.

In the UK normative sample, verbal intelligence was estimated from the National Adult Reading Test (NART, (141)). The NART required subjects to pronounce a set of irregular nouns (in which the pronunciation could not be inferred directly from the spelling). It has been validated as a brief measure of verbal intelligence. It is acknowledged that intelligence estimate of the Chinese and Caucasian sample were based on different measures. Direct comparison between intelligence levels between

the two samples was avoided.

4 Samples characteristics and descriptive results

Introduction

In this Chapter a detailed description of the recruitment and inclusion criteria, as well as the basic characteristics and descriptive statistics for neurological signs scores for each of the samples shall be provided.

The following core inclusion and exclusion criteria were used in all the studies unless otherwise specified.

Recruitment criteria

Recruitment criteria were considered based on information from interview with patients and medical records.

Inclusion Criteria

For schizophrenic patients

- Age 18 to 65 with DSM-III-R/IV criteria for schizophrenia (study 4 employed DSM-IV criteria, schizoaffective and schizophreniform patients were also recruited in study 4)

For control subjects

- Age 18 to 65 with no personal history of schizophrenia

Exclusion Criteria

- Neurological or serious medical illnesses such as epilepsy, head injury, stroke, diabetes, and endocrine disorder
- History of regular substance abuse
- History of ECT within 6 months
- Inability to give informed consent for the study

Study 1

Healthy control subjects

Subjects in the normative sample in Hong Kong were unpaid volunteers recruited through a series of public education events. The events were announced publicly and were free of charge. Participants either obtained prior registration or walk in to the venue. Potential subjects were screened with a structured questionnaire for exclusion criteria (see above). In addition to the CNI and cognitive function tests, subjects were assessed using the Information subscale in the WAIS-R HK in order to arrive at an estimate of intelligence level.

A total of 94 subjects (32 males and 62 females) were recruited. The mean age and education level was 38.3 years (SD = 12.9) and 8.9 years (SD = 3) respectively.

Schizophrenic Patients

Subjects with a clinical diagnosis of schizophrenia were invited to be considered for participation from 3 inpatients units in Hong Kong (KCH, QMH, LCKH, see appendix 1). KCH and QMH contained acute inpatient units. KCH and LCKH contained chronic rehabilitation units. The sample thus consisted of a mixture of patients in different stages in the course of the illness. Research diagnosis was made by consensus involving two experienced clinicians according to DSM-III-R criteria, making use of clinical interview and information from case records and informants.

Subjects recruited into the study received a more extensive clinical and cognitive evaluation in addition to neurological signs assessments.

The sample consisted of 195 patients (120 males and 75 females). One hundred and eighty four patients were right handed, 4 were left handed, and 7 were mix-handed (handedness was determined using the Annett scale (142)). The mean age was 39.7 years (SD = 12.1). The number of years of education was 8.1 years (SD = 3.5). The mean illness duration was 14.7 years (SD = 9.7). The mean anti-psychotics dosage (chlorpromazine equivalence) was 922.13 mg/day (SD = 917.47). The mean daily dosage of anti-cholinergic was 3.28 mg of benzhexol (SD = 3.34). Benzhexol was the only anti-cholinergic medication encountered in the sample. Study 1 CNI subscale scores for patients and healthy controls are presented in Table 4.1. Prevalence of individual signs are presented in Appendix 3a

Table 4.1. SNS subscale scores in Chinese patients and healthy control subjects

CNI subscale	Normal control subjects (n = 94)		Schizophrenic patients (n= 195)	
SNS subscale	*Mean*	*SD*	*Mean*	*SD*
Motor coordination **	10.64	14.38	20.61	25.66
Sensory integration **	9.41	11.31	20.90	30.05
Disinhibition *	10.11	12.33	15.56	14.13

*p<0.01; **p<0.001, unpaired t-tests, Non-parametric Man-Whitney U-tests produced similar significant levels

Study 2

Healthy subjects (Caucasian)

The normative sample was obtained through recruitment of paid healthy volunteers from employees of a large commercial institution based at Cambridge. Recruitment was effected by internal advertisement within the institution. Participants were screened for inclusion and exclusion criteria (see above) using a standard questionnaire. In addition to the CNI subjects were also evaluated with the National Adult Reading Test (NART, Nelson, 1982) to arrive at an estimate of the general intelligence level.

In the 80 subjects recruited there was a male preponderance (65 males, 15 females). Handedness was assessed clinically (70 right-handed, 8 left-handed, 2 mixed). The mean age was 42.0 years (s.d. 13.7 years). The IQ estimates (WAIS-R) was 112.5 (SD = 6.5).

Chronic schizophrenic patients (Caucasian)

Patients with chronic schizophrenia were recruited from an inpatient rehabilitation unit at Fulbourn Hospital, Cambridge. Diagnosis of schizophrenia was made according to DSM-III-R criteria by an experienced research psychiatrist (PJM). Subjects were assessed with the CNI after giving informed verbal consent.

The sample consisted of 52 patients (34 male and 18 female). 45 were right-handed,

7 were left-handed. Mean age was 39.3 (sd 11.0). Mean illness duration was 17.1 years (sd 11.8). The mean dosage of medication (daily chlorpromazine equivalent) was 1728 mg/day (SD = 2699). It was noted that this represents a relatively high antipsychotics dosage and may reflect the lack of pharmacological options for the severely unwell patients necessitating long-term hospitalization in a period before clozapine or atypical antipsychotics became more widely used. CNI Subscale scores for Caucasian patients and healthy controls are shown in Table 4.2. SNS item prevalences are shown in appendix 3b.

Table 4.2. SNS subscale scores in Caucasian patients and healthy control subjects

	Normal control subjects (n = 80)		Schizophrenic patients (n = 52)	
SNS subscale	*Mean*	*SD*	*Mean*	*SD*
Motor coordination**	6.39	10.43	43.97	29.48
Sensory integration**	16.25	17.27	42.33	26.31
Disinhibition**	6.09	9.33	18.75	15.08

*p<0.01; **p<0.0001, unpaired t-tests, Non-parametric Man-Whitney U-tests produced similar significant levels

Study 3

Study 3 was a longitudinal study of SNS in patients with chronic schizophrenia. 38 patients fulfilling inclusion criteria from LCKH were follow-up three years after the initial assessment and a repeated assessment of their cognitive function and neurological signs were carried out. In addition to the core inclusion and exclusion

criteria, patients had to be clinically stable (i.e. not in relapse) at the time of the study.

The sample consisted of 29 males and 9 females. The mean age was 47.3 years (SD = 7.2) and the mean education level was 6.7 years (SD = 2.9). The mean illness duration was 25.9 years (SD = 9.4) at the beginning of the study. Average dosage of conventional antipsychotic medication was 844 mg chlorpromazine equivalence per day (SD = 691), and the average dosage of anticholingeric medication (Benzhexol) was 4 mg (SD = 3). At follow up, the average daily dosage of antipsychotic medication was 829 mg chlorpromazine equivalence per day (SD = 688), and the average dosage of anticholingeric medication was 5 mg (SD = 3). Study 3 subscale scores are shown in Table 4.3. Item prevalences are shown in appendix 3c.

Table 4.3. Longitudinal comparison of SNS among Chronic patients

	Baseline	3 year follow-up	Paired t-tests
SNS subscales	*Mean (SD)*	*Mean (SD)*	*p-value*
Motor coordination (n = 36)	22.86 (28.64)	29.84 (31.4)	0.0321
Sensory integration (n = 25)	14.5 (21.25)	25.5 (22.09)	0.0364
Disinhibition (n = 26)	13.46 (13.66)	28.85 (19.29)	0.0002

Study 4

Study 4 was a longitudinal study of motor SNS in first episode schizophrenia, schizophreniform psychosis and schizoaffective psychosis. Consecutive subjects were recruited from a defined catchment area (Hong Kong Island and off shore

Islands). Subjects presented with a psychotic disorder for the first time to outpatient or inpatient services based at QMH and PYNEH (Appendix I). DSM-IV diagnoses were made using the SCID. Clinical and cognitive assessment, as well as an abridged version of the CNI (covering mostly motor coordination signs) was employed in the study. Subjects were assessed as soon as possible after contact, and then again after the psychotic symptoms were stabilized. They were then followed up longitudinally on a four-monthly basis. At the time of writing, all subjects have been followed up for at least 2 years after stabilization from the first episode.

Data from 68 patients (30 male and 38 female) with initial diagnosis of schizophrenia, schizophreniform psychosis or schizoaffective disorder are analyzed. The mean age was 32.9 (s.d. 9.5) years. Average duration of untreated psychosis (DUP) was 562 days (s.d. 906, in 7 subjects the DUP could not be reliably ascertained). The DSM-IV diagnoses and medication are presented in the Tables 4.4 and 4.5.

Table 4.4. Diagnoses in first episode patients

SCID Diagnosis	Percentage
Schizophrenia-disorganized type	1 (1.5%)
Schizophrenia-paranoid type	28 (41%)
Schizoaffective disorder	2 (3%)
Schizophreniform disorder	28 (41%)
Schizophrenia-Undifferentiated type	9 (13.5%)

Table 4.5. Medication dose prescribed for first episode patients

	Schizophrenia (n = 68)			
	Initial contact		Clinical stablization	
	Mean	*SD*	*Mean*	*SD*
Chlorpromazine equivalence (mg/day)	171.97	490.17	348.49	352.31
Benzhexol (mg/day)	5.92	5.95	5.3	2.94

Clozapine at stabilization n = 1, Risperidone at stabilization n = 5, Benzhexol at stabilization n = 43

A matched control group was drawn from a larger pool of normative data from study 1 (see above) so that the age and the education level matched those in the patient group. Table 4.6 shows that the mean age for the 68 normal subjects (22 males, 46 females) was 32 years (SD = 8.4), and the number of years of education was 9.4 years (SD = 2.6). There was no significant difference between patients and controls in these variables. In addition, 34 patients were assessed in a medication-naïve state (50%), the rest were assessed within 7 days of starting medication. They do not differ significantly on the demographic variables (Table 4.7).

Table 4.6. Demographic variables for first episode patients and healthy control subjects

	Schizophrenia (n = 68)		Matched controls (n = 68)	
	Mean	*SD*	*Mean*	*SD*
Age	32.9	9.5	32.0	8.4
Education level (years)	10.2	3	9.4	2.6
Gender (M:F)	30 : 38		22:46	

Table 4.7. Comparison of motor coordination signs between recently-medicated patients and medication-naïve patients

	Medication-naïve patients (n = 34)		Recently-medicated patients (n = 34)	
	Mean	*SD*	*Mean*	*SD*
Age	32.7	9.2	33.1	9.9
Education level (years)	9.9	3	10.4	2.9
Gender (M:F)	15:19		15:19	
Motor subscale score	1.68	2.06	1.79	1.97

The CNI subscale scores at the initial assessment are summarized below (Table 4.8). The basic scores for the patients at first assessment were listed separately for those who were assessed in medication-naïve state and those assessed after they have been recently medicated (Table 4.9). Item prevalences are presented in appendix 3d.

Table 4.8. Comparison between patients and healthy control subjects

	First episode patients		Matched controls	
	Mean	*SD*	*Mean*	*SD*
Motor subscale*	1.74	2.00	0.85	1.33

*p<0.003, unpaired t-test

Table 4.9. SNS comparison between medication-naïve patients, recently-medicated patients and healthy control subjects at initial presentation

	Medication-naïve patients (n = 34)		Recently-medicated patients (n = 34)		Matched controls (n = 68)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Motor subscale score*	1.68	2.06	1.79	1.97	0.85	1.33

*p<0.05 for both ANOVA and Kruskal-Wallis Test between medicated cases and normal control subjects

5 Demographic and clinical correlates of SNS

Introduction

This chapter describes a study of the relationships between SNS and key demographic variables: age, gender, ethnicity, education level and intelligence level, as well as illness duration and clinical correlates. The relationship between age and SNS is a complex issue in cross sectional studies as it is confounded by illness duration. Additional analyses to evaluate the relative importance of age and illness duration are attempted.

Education and intelligence level, and gender effects

The relationship between SNS, education level, intelligence level, as well as gender is explored within each healthy control subjects and patients groups in studies 1 and 2. Further data of interest from studies 3 and 4 (not primarily addressing these issues) will be presented in later chapters.

Chinese healthy control subjects

In the Chinese control sample, lower education level is modestly but significantly correlated with increased motor coordination signs (rho = -0.34, p = 0.001) (Table 5.1). Older age tends to correlate with motor soft neurological signs (rho = 0.21, p = 0.05). Verbal IQ estimates were also significantly correlated with motor soft neurological signs (rho = -0.26, p = 0.04) and sensory integration signs (rho = -0.33, p = 0.008). The modest but significant correlation between age and motor SNS in the

control group is notable as this relationship is not complicated by the confounding variables of age of onset and illness duration as in the patient sample (see below).

Table 5.1. Correlations between soft neurological signs and demographic variables among healthy control subjects

	Correlation coefficients	Motor coordination	Sensory integration	Disinhibition
Age	*Pearson*	0.13	0.09	0.13
	Spearman	0.21*	0.06	0.16
Education level	*Pearson*	-0.35****	-0.23*	-0.17
	Spearman	-034****	-0.18	-0.22
Intelligence level	*Pearson*	-0.3*	-0.33**	-0.22
	Spearman	-0.26*	-0.33**	-0.18

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001

Comparison between SNS in male and female healthy subjects initially revealed that significantly more motor coordination signs were found in female subjects in the Chinese normal sample (Table 5.2). Male and female subjects appeared to be matched for age but female subjects had a lower education level. Since SNS scores may co-vary with education level, an ANCOVA controlling for education level was conducted with SNS scores as dependent variables. No significant difference was found in sensory integration [$F(1,91) = 2.329$, $p>0.05$], disinhibition [$F(1,91) = 0.33$, $p>0.05$], and total soft signs [$F(1,91) = 1.327$, $p>0.05$]. However there was a persisting trend for female subjects to have higher motor coordination signs than their male counterparts [$F(1,91) = 4.665$, $p = 0.03$] (significance level after multiple comparison correction = 0.0125).

Table 5.2. Comparison between male and female Chinese healthy control subjects

	Male (n = 32)		Female (n = 62)				
	Mean	*SD*	*Mean*	*SD*	*t-value*	*df*	*p-value*
Age	39.8	13.9	37.6	12.3	0.81	92	0.4188
Education level	9.5	3.1	8.6	2.93	1.40	92	0.1657
Motor coordination	5.6	10.6	13.2	15.4	-2.84	91	0.0055
Sensory integration	8.5	12.2	9.9	10.9	-0.56	91	0.5733
Disinhibition	9.4	13.5	10.5	11.8	-0.41	92	0.6819
Total soft signs score	22.0	23.8	33.6	27.2	-2.02	91	0.0455

Chinese schizophrenic patients

Amongst Chinese schizophrenic patients motor coordination and disinhibition signs were correlated with age, intelligence level, and illness duration (see Table 5.3). All SNS were correlated with education and intelligence levels. This is supported by both parametric and non-parametric analyses.

Table 5.3. Correlations between neurological signs and demographic variables among Chinese patients

	Correlation Coefficients	Motor coordination	Sensory integration	Disinhibition
Age	*Pearson*	0.31****	0.14	0.20**
	Spearman	0.30****	0.08	0.19
Education level	*Pearson*	-0.33****	-0.33****	-0.25****
	Spearman	-0.33****	-0.31****	-0.22***
Intelligence level	*Pearson*	-0.46****	-0.45****	-0.35****
	Spearman	-0.47****	-0.55****	-0.36****
Duration of illness	*Pearson*	0.31****	0.12	0.22***
	Spearman	0.30****	0.11	0.23****

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001

In Chinese schizophrenic patients, male and female subjects do not appear to differ in the SNS scores after multiple group comparison adjustment. Non-parametric Wilcoxon test indicated similar results (Table 5.4).

Table 5.4. Comparison between male and female Chinese patients

	Male (n=120)		Female (n = 75)				
	Mean	*SD*	*Mean*	*SD*	*t-value*	*df*	*p-value*
Age	40.4	12.0	39.5	12.6	0.540	191	0.5898
Education level (year)	8.2	3.3	7.9	3.6	0.488	188	0.6264
Duration of illness (year)	15.7	9.9	14.1	9.6	1.160	193	0.2473
Chlorpromazine equivalence (mg/day)	822	777	1168	1296	-2.091	191	0.0389
Benzhexol (mg/day)	3.07	3.11	3.73	3.72	-1.344	192	0.1804
Motor coordination	18.3	24.8	24.3	26.7	-1.597	191	0.1118
Sensory integration	18.0	21.1	25.6	40.3	-1.632	176	0.1045
Disinhibition	13.8	13.0	18.2	15.4	-2.001	133.32	0.0475
Total soft signs score	48.23	46.83	65.93	7.99	-2.078	171	0.039

Caucasian healthy control

Table 5.5 summarizes the correlations between demographics and soft neurological signs. In healthy Caucasian subjects, lower intelligence level is associated with increased motor coordination (rho = -0.27, p = 0.02) and sensory integration soft signs. Increased motor soft signs are also correlated with older age. The same pattern is found with non-parametric analysis. There appears to be no significant gender effect on SNS as shown in Table 5.6. This conclusion is however limited by a

relatively small sample size for female subjects (n=15).

Table 5.5. Correlations between soft neurological signs and demographic variables among Caucasian healthy control subjects

	Correlation coefficients	Motor coordination	Sensory integration	Disinhibition
Age	*Pearson*	0.29**	0.11	0.1
	Spearman	0.30**	0.13	0.06
Intelligence level	*Pearson*	-0.30**	-0.32***	-0.22
	Spearman	-0.27*	-0.34***	-0.18

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001

Table 5.6. Comparison of prevalence of neurological signs between male and female Caucasian healthy control subjects

	Male (n = 65)		Female (n = 15)				
	Mean	*SD*	*Mean*	*SD*	*t-value*	*df*	*p-value*
Motor coordination	5.6	9.0	9.6	15.1	-0.985	78	0.339
Sensory integration	16.9	17.6	13.3	16.0	0.723	78	0.472
Disinhibition	5.6	9.1	8.3	10.2	-1.032	78	0.305
Total SNS	28.1	25.6	26.5	6.8	-0.428	78	0.67

Caucasian schizophrenic patients

Amongst Caucasian patients, no significant correlation was found between SNS and either age or illness duration (Table 5.7). Medication dosages were inversely correlated with disinhibition signs ($r = -0.31, p<0.05$; rho = -0.32, $p<0.05$). As in the control subjects, there were no gender differences in the prevalence of neurological signs in Caucasian schizophrenic patients (Table 5.8).

Table 5.7. Correlations between soft neurological signs, age, duration of illness and medication

	Correlation coefficient	Motor coordination	Sensory integration	Disinhibition	Total soft signs score
Age	*Pearson*	0.17	0.12	0.09	0.07
	Spearman	0.12	0.04	0.12	-0.02
Duration of illness	*Pearson*	0.12	0.14	0.2	0.05
	Spearman	0.04	0.01	0.22	-0.06
Medication	*Pearson*	-0.10	-0.02	-0.31*	-0.2
	Spearman	-0.20	0.18	-0.32*	-0.17

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001

Table 5.8. Comparison of prevalence of neurological signs between male and female Caucasian patients

	Male (n = 34)		Female (n = 18)				
	Mean	*SD*	*Mean*	*SD*	*t-value*	*df*	*p-value*
Age	40.0	11.4	37.9	10.7	0.6606	50	0.5119
Duration of illness	18.0	10.7	15.8	8.3	0.7165	40	0.4778
Chlorpromazine equivalence (mg/day)	2031.4	3041.9	1155.1	1835.7	1.1163	50	0.2696
Motor coordination	44.1	28.1	43.8	32.7	0.0313	45	0.9752
Sensory integration	45.5	27.9	36.8	23.0	1.0714	42	0.2901
Disinhibition	17.9	15.8	20.1	14.3	-0.4966	44	0.6219
Total soft signs score	103.2	55.6	95.8	49.7	0.4298	37	0.6698

Summary of key findings

On the whole there are significant associations between most SNS subgroups and age, verbal intelligence, as well as education level. Amongst the SNS subscales the relationship between motor coordination and age appears most robust. There is a suggestion of gender effect (more SNS in female subjects in the HK control sample)

but this might be related to sampling bias and will require further studies to confirm.

Ethnicity effects

SNS scores from normative samples from study 1 (Chinese) and study 2 (Caucasian) were compared, taking into consideration potential confounding effects of other variables. Scores from patient samples could not be directly compared as the clinical state of the two patient samples were not directly comparable.

Demographic characteristics in normative samples

Table 5.9. Comparison of demographic variables between Caucasian and Chinese healthy control subjects

	Caucasian normal control subjects (n = 80)		Chinese normal control subjects (n = 94)	
	Mean	*SD*	*Mean*	*SD*
Age	42.09	13.68	38.34	12.87
Intelligence level	112.5	6.5	95.3	8.6
Education level	N/a	N/a	8.87	2.99
Gender (M:F)	65:15		32: 62	

Table 5.9 shows that no significant difference was found between the Caucasian and Chinese normative samples in age ($t(172) = 1.859$, $p>0.05$). However, the Chinese sample comprised significantly more female subjects than their Caucasian counterparts (chi-square (1) = 39.041, $p <0.0005$).

Soft neurological signs in normative samples

Analyses of subscales scores show that Chinese healthy subjects tended to score higher in the motor coordination and the disinhibition subscales, whereas Caucasian healthy subjects tended to score higher in the sensory integration subscale (Table 5.10).

Table 5.10. Prevalence of SNS between Caucasian and Chinese healthy control subjects

	Caucasian normal (n = 80)		Chinese normal (n = 94)				
	Mean	*SD*	*Mean*	*SD*	*t-value*	*df*	*p-value*
Motor coordination	6.39	10.43	10.64	14.38	-2.252	167.9289	0.0256
Sensory integration	16.25	17.27	9.41	11.31	3.028	132.5478	0.0030
Disinhibition	6.09	9.33	10.11	12.33	-2.439	169.7467	0.0157

Analyses of covariance (ANCOVAs) were carried out between Chinese and Caucasian healthy control subjects, controlling for age and intelligence. In this analysis there was no significant ethnicity effect on the total SNS scores. Analyses of subscales scores however suggest that after correction for multiple comparisons, there was a trend [$F(1,161) = 5.80$, $p=0.017$] for Caucasian healthy subjects to have higher sensory integration signs than their Chinese normal counterparts.

Summary of findings

There is no significant difference in total SNS scores between normal Chinese and Caucasian subjects. However there was a trend for Chinese subjects to have lower score in the sensory integration subscale.

Clinical correlates

The relationship between SNS and clinical picture was explored by correlation analysis between each subgroup of SNS and individual items in clinical symptom rating scales. Table 5.11 summarizes the relationships between neurological soft signs and symptoms. When the entire sample was considered, modest correlations were found between motor coordination and HEN speech domain (rho = 0.16, $p<0.05$) and HEN thought domain (rho = 0.2, $p<0.01$). These correlations however become trends upon corrections for multiple comparisons.

In addition, motor coordination was also inversely correlated with anxiety factor of the BPRS (rho = -0.25, $p<0.001$). Sensory integration and disinhibition were inversely correlated with positive symptoms of BPRS ($r = -0.18$, $p<0.05$). Disinhibition was also inversely correlated with positive symptoms of BPRS ($r = -0.155$, $p<0.05$). Once again, all these relationships would become trends after corrections for multiple comparisons.

When correlation analysis is carried out separately for male and female subjects an interesting pattern emerged. In female patients, the "thought" domain of the negative symptom scale HEN was significantly correlated with motor coordination ($r = 0.37$, $p = 0.001$), with sensory integration ($r = 0.36$, $p = 0.003$), as well as total SNS (rho = 0.42, $p = 0.0005$). In contrast, there was no significant correlation between SNS and HEN symptom domains in male patients.

Summary of findings

Correlation between SNS and symptoms are modest. However, when males and females subjects were considered separately, there is a significant correlation between SNS and "thought" subscale of the negative symptom rating scale HEN.

Table 5.11. Symptom correlates of neurological soft signs in patients

	HEN Appear-ance	HEN Behavior	HEN Speech	HEN Thought	HEN Affect	HEN Function-ing	BPRS negative symptom	BPRS positive symptom	BPRS affective symptom	BPRS anxiety	BPRS thought
MC											
All patients	0.06	0.04	0.18*	0.17*	0.11	0.08	0.08	-0.17*	-0.04	-0.20*	-0.06
Male	0.08	-0.03	0.19*	0.09	0.08	0.16	0.14	-0.17	-0.11	-0.22*	-0.16
Female	0.08	0.18	0.24*	0.37***	0.20	0	0.07	-0.24*	0.07	-0.17	0.02
SI											
All patients	0.03	0.01	0.09	0.13	-0.02	0.04	0.02	-0.18	-0.06	-0.13	-0.08
Male	0.02	-0.12	0	0.03	-0.08	-0.06	-0.02	-0.26**	-0.10	-0.10	-0.12
Female	0.08	0.17	0.25*	0.36***	0.09	0.16	0.16	-0.20	-0.04	-0.18	-0.08
DI											
All patients	0.08	-0.04	0.10	0.08	-0.04	0	0.03	-0.12	0.06	-0.13	0.04
Male	0.23*	-0.03	0.18	0.13	0.02	0.12	0.06	-0.09	0.04	-0.11	-0.07
Female	-0.05	-0.03	0.05	0.08	-0.06	-0.13	0	-0.32**	0.06	-0.04	0.12
Total SNS											
All patients	0.10	0.02	0.13	0.18*	0.04	0.07	0.04	-0.19*	-0.02	-0.17	-0.05
Male	0.11	-0.10	0.10	0.13	0	0.07	0.06	-0.22*	-0.08	-0.17	-0.16
Female	0.15	0.22	0.29*	0.42***	0.15	0.11	0.15	-0.25*	0.04	-0.17	0.01

MC, motor coordination; SI, sensory integration; DI. Disinhibition. *p<0.05, **p<0.01, ***p<0.005, ****p<0.001, Pearson correlation coefficient

Age and illness duration effects

In this Section a more detailed exploration of the relationship between SNS and the variables "age" and "illness duration" is attempted. The use of a cross sectional sample has inherent limitations in addressing these issues, however it has the advantage of being able to cover a wide range of different ages and illness durations. Since longitudinal studies addressing a long follow-up period (spanning decades) is difficult to carry out, as much information as possible should be extracted from analyses of cross sectional samples. Longitudinal studies addressing specific stages of the illness, with shorter follow-up periods (2 to 3 years) will be presented in later Chapters.

Simple correlations between age and SNS have been presented in the previous sections. Correlation coefficients however would be compromised if there were non-linearity in the relationship between SNS and age or illness duration. For instance, the relationship between the variables could be more pronounced at a particular age range, rather than over the entire age range. Attempt was made to address this by grouping subjects according to age or illness duration, and then making comparisons between the groups.

In the first stage of the analysis, effect of age was assessed by stratifying the sample into groups of different ages and then comparing the level of SNS between them. Following this, patients are re-categorized into groups of different illness duration

and their levels of SNS are compared. A further comparison was carried out by contrasting SNS in groups of younger and older patients with long and short illness durations.

Age effects

Patients and healthy controls were assigned to four groups according to age (16-25, 26-35, 36-45, >45). ANOVA with linear trend analysis was first carried out to ascertain if there were linear and non-linear relationships between SNS scores and age. F value and p value for the weighted linear term were reported. This was followed up with ANCOVA for patient and for control groups separately using education level as a covariate, and SNS scores as dependent variables.

Characteristics of patients in each group are summarized in Table 5.12 below. The four groups did not differ significantly in terms of gender proportion (chi-sq (3) = 1.01, $p>0.05$) and medication [$F(3,190) = 1.13$, $p>0.05$]. However, significant differences were found in education level among the four groups [$F(3,186) = 6.19$, $p<0.0005$]. Post-hoc analyses showed that Group IV (age >45) was significantly less educated than Group I (age 16-25) ($p<0.03$) and Group II (age 26-35) ($p<0.003$).

In addition, as expected, differences were found in illness duration between the groups [$F(3,191) = 55$, $p<0.0005$]. Post-hoc analyses indicated that Group I (age 16-25) had a significant shorter illness duration than Group III (age 36-45) ($p<0.0005$) and Group IV (age >45) ($p<0.0005$). At the same time, Group II (age 26-35) also had

significant short illness duration than Group III (age 36-45) ($p<0.0005$) and Group IV (age >45) ($p<0.0005$), whereas Group III (age 36-45) had significant shorter illness duration than Group IV (age >45) ($p<0.0005$).

Table 5.12. Comparisons of demographic variables among different age groups in patients

	Group I (age 16-25) (n = 26)		Group II (age 26-35) (n = 45)		Group III (age 36-45) (n = 51)		Group IV (age 46 +) (n = 64)		F-value	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Chi-sq*	*p-value*
Age	22.1	2.9	30.1	2.7	39.7	2.5	53.4	5.7	515.21	*<0.0005*
Gender (M:F)	16 : 10	--	25 : 20	--	31 : 20	--	40 : 24	--	1.01	*0.799*
Duration of illness (year)	4.1	3.4	8.8	5.6	15.8	6.9	22.3	9.1	55	*<0.0005*
Education level (year)	9.3	1.8	9.4	2.9	7.7	3.6	6.9	3.7	6.19	*<0.0005*
Chlorpromazine equivalence (mg/day)	884.6	953.8	818.3	768.8	1204.5	1103.3	788.6	808.5	1.13	*0.338*
Benzhexol (mg/day)	2.46	2.85	3.5	3.9	3.7	3.3	3.2	3.1	0.72	*0.543*

Group I: age 16-25; Group II age 26-35; Group III age 36-45; Group IV age >45

Analysis of variance with linear trend analysis revealed that there was a significant linear trend increase in total SNS across age groups [weighted linear term, $F(1,169) = 5.2$, $p=0.023$]. Subscale scores analysis showed that the increase was found in the motor coordination [weighted linear term, $F(1,189) = 12.5$, $p=0.003$] and disinhibition subscales [weighted linear term, $F(1,180) = 5.46$, $p = 0.02$] but not in the sensory integration subscale [weighted linear term, $F(1,174) = 2.16$, $p=0.42$] (Figure 5.1). Since significant differences were found among the age groups in terms of education

level [$F(3,186) = 6.193$, $p<0.0005$]. ANCOVA was carried out to control for education level. After this adjustment, no significant difference was found among age groups as a whole [$F(3,183) = 2.377$, $p <0.1$], post-hoc analysis indicated however that the 16-25 age group had significantly lower motor coordination signs than others groups ($t = 2.088$, $p = 0.038$) and group above 45 years had significantly higher motor signs than the rest ($t=2.222$, $p = 0.027$). The other soft sign subscales and total soft signs scores did not differ significantly across age groups.

These results indicate increase in motor coordination signs and disinhibiton signs with older age. However this is complicated by the tendency towards lower education level in these groups. The relationship with age was no longer significant in further analysis of covariance taking into consideration of education level. Thus on the whole the data did not suggest an unequivocal deterioration of soft signs associated with age across a wide age span. A noteworthy remark is that post hoc analysis identified that at the extremes of ages; there may be a difference in motor coordination signs (the youngest patients have less, and the oldest patients have more, but patients in between are not significantly different from one another). This possibility cannot be ruled out since any such specific effects at either ends of the age range would have been "diluted" by relative stability of SNS levels in the middle age ranges.

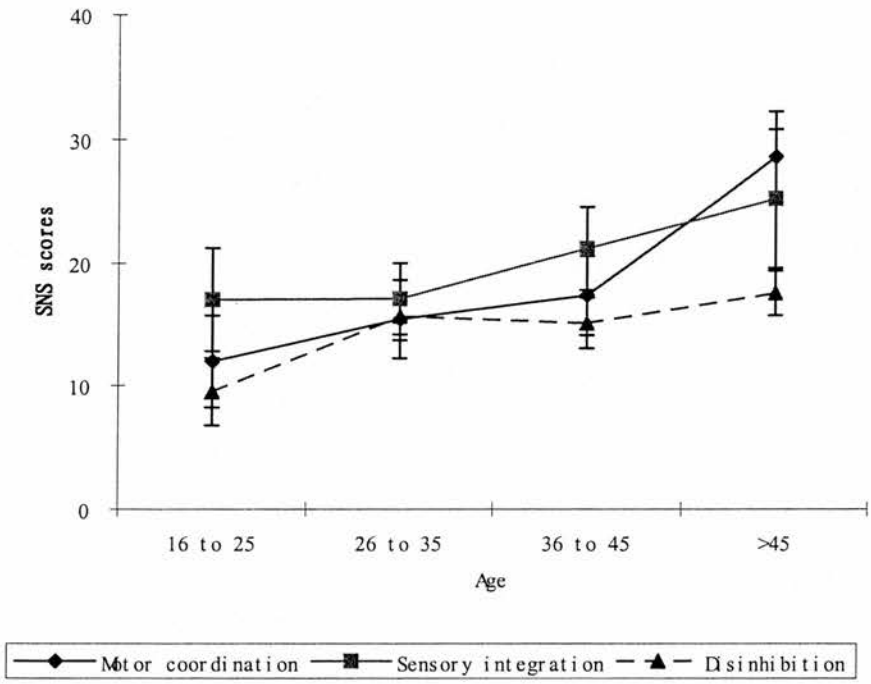


Figure 5.1: The prevalence of soft neurological signs among different age groups

To summarize, this initial analysis suggests that there is a trend for SNS (total SNS, motor coordination and disinhibition) increase associated with age. However, the relationship with age became non-significant after controlling for education level.

Illness duration effects

Similar to the analysis of age, patients were categorized into six groups according to illness duration (Group I: less than 5 years; Group II: 6-10 years; Group III: 11-15 years; Group IV: 16-20 years; Group V: 21-25 years; Group VI: more than 25 years). The six groups did not differ significantly in terms of gender proportion (chi-square

(5) = 2.37, p>0.05) and medication dosage [F(5,188) = 1.85, p>0.05] (Table 5.13).

ANOVA on duration of illness with linear trend analysis was conducted. F value and p-value for the weighted linear term were reported. Characteristics of patients in illness duration groups are summarized in the table. Significant differences were found among the groups in terms of age [F(5,187) = 29.27, p<0.0005] and education level [F(5,184) = 4.41, p= 0.001].

Post-hoc analyses indicated that Group I was significantly younger than Group III (p = 0.001), Group IV (p<0.0005), Group V (p<0.0005), and Group VI (p<0.0005). Group II was also significantly younger than Group IV (p<0.0005), Group V (p<0.0005), and Group VI (p<0.0005). Group III was significantly younger than Group V (p<0.001), and Group VI (p<0.0005). At the same time, Group VI had significantly lower education level than Groups I and II.

Table 5.13. Comparison of demographic variables among different illness duration groups

	Group I (n=39)		Group II (n=33)		Group III (n=37)		Group IV (n=26)		Group V (n=23)		Group VI (n=28)			
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	F-value *chi-sq*	*p-value*
Age	29.4	10.3	33.1	8.7	37.3	9.1	45.5	9.5	48.3	7.5	52.0	7.5	29.27	<0.0005
Education level	9.4	2.9	9.1	3.1	7.2	2.9	8.0	4.0	8.1	3.3	6.1	3.9	4.41	0.001
Gender (M:F)	21:18		21:12		22:15		19:7		15:8		19:9		2.37	0.80

Group I: illness duration 0-5; Group II illness duration 6-10; Group III illness duration 11-15; Group IV illness duration 16-20; Group V illness duration 21-25; Group VI illness duration >25

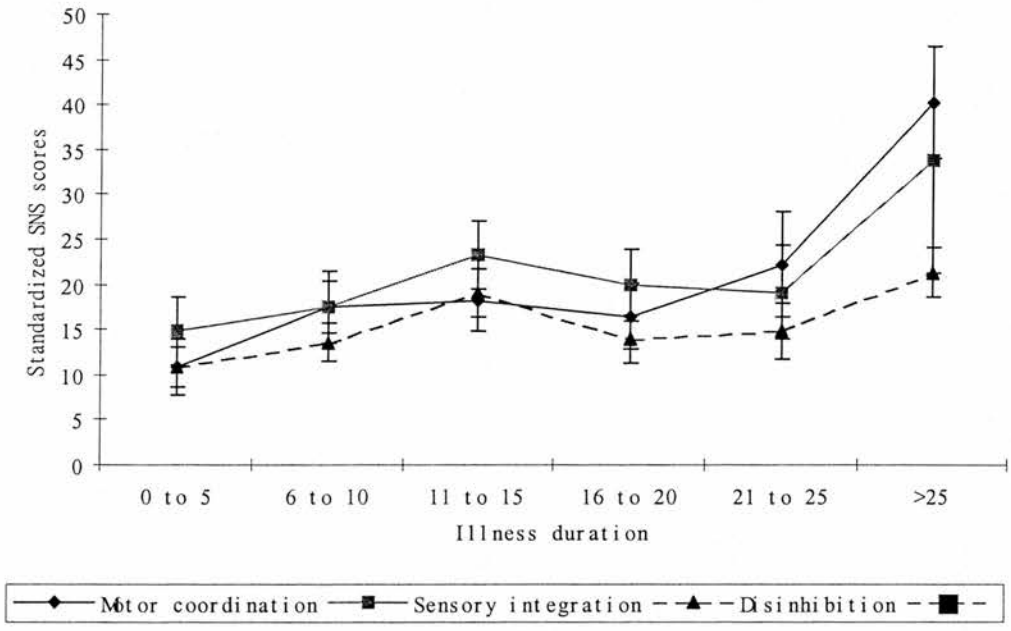
ANOVA with linear trend analysis revealed that there was a significant linear

increase in total SNS associated with longer illness duration [weighted linear term $F(1,167) = 13.3$, $p=0.0004$]. Amongst the subscales, motor coordination signs increased as the duration of illness increased [weighted linear term $F(1, 187) = 18.86$, $p<0.00005$]. There was a trend increase for sensory integration signs [weighted linear term $F(1,172) =4.0$, $p = 0.04$] and disinhibition signs [weighted linear term $F(1,178) =7.8$, $p = 0.015$]. However, they became non-significant after correction for multiple comparisons.

ANCOVAs were also carried out using SNS scores as dependent variables, illness duration as the independent class variable, controlling for education level. Significant difference was still found in motor coordination signs among groups [$F(5,181) = 3.677$, $p= 0.003$]. Post hoc analysis revealed that patients with 16-25 years of illness had significantly lower motor coordination signs than others and those with over 25 years illness duration had significantly higher motor signs than the rest. The other soft sign subscales and total soft signs scores did not differ significantly across illness-duration groups.

This analysis shows that motor coordination signs increase with illness duration, even after controlling for education level and accounting for multiple comparisons.

Figure 5.2: The prevalence of soft neurological signs among different illness duration groups



Subgroups with different illness duration and age

In a further examination of the relative effects of age and illness duration, patients are assigned into one of the following four subgroups, Group I (n=16) consists of those with older age (>38) but a shorter illness duration (<12); Group II (n=17) consists of those with younger age (<38) but a long illness duration (>12); Group III (n = 74) consists of those with older age (>38) and a longer duration of illness (>12); Group IV (n = 61) consists of those with younger age (<38) and shorter illness duration (n = 12). One-way ANOVA was conducted among these groups (Table 5.14). Post hoc comparisons between individual groups were also carried out. In addition, a further analysis controlling for education level was conducted.

Table 5.14. Comparisons of demographic characteristics and SNS among patient groups with different age and illness duration

	Group I Older Shorter ID (n = 16)		Group II Younger Longer ID (n = 17)		Group III Older Longer ID (n = 74)		Group IV Younger Shorter ID (n = 61)			
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	F-value	p-value
Education level	8.25	2.79	6.94	1.85	7.58	3.69	9.82	2.47	7.4762	0.0001
Intelligence estimate	7.44	2.76	6.00	1.97	6.04	2.75	7.25	2.57	3.2126	0.0245
Motor coordination	7.64	13.89	18.30	22.20	26.43	28.30	13.30	20.57	4.71	0.0035
Sensory integration	12.19	11.79	24.26	13.60	25.00	40.54	17.21	21.43	0.458	0.712
Disinhibition	8.59	10.92	22.06	12.91	16.89	15.40	11.89	12.38	4.16	0.007
Total soft signs score	28.42	23.02	64.62	32.87	68.32	67.98	42.40	43.97	4.08	0.008

ID: illness duration, Group I: Age>=38 & Du<=12; Group II: Age<38 & D>12; Group III: Age>=38 & Du>12; Group IV: Age<38 & Du<=12

Significant differences were found among the groups in terms of education level ($F = 7.48$, $p<0.0001$) and information subscale ($F = 3.21$, $p = 0.025$). Post-hoc analyses indicated Group IV had significantly higher education level than Group II ($p = 0.004$) and Group III ($p = 0.0002$). Group IV also received more education than Group III ($p = 0.05$).

In the neurological soft signs, significant differences were found among the groups in motor coordination ($F = 4.7$, $p = 0.0035$), disinhibition ($F = 4.16$, $p = 0.007$), and total soft signs scores ($F = 4.08$, $p = 0.008$).

Post-hoc analyses indicated that Group III (older and longer illness duration) exhibited significantly more motor coordination signs and total soft signs score than Group I (older but shorter illness duration) ($p = 0.03$; $p = 0.05$, respectively), and Group IV (younger and shorter illness duration) ($p = 0.01$; $p = 0.04$, respectively); but was not significantly different from Group II (Younger but longer illness duration). This would suggest that for total SNS and motor coordination signs, illness duration has a more important effect than age *per se*.

Likewise for disinhibition signs, Group II (younger age with longer illness duration) demonstrated significantly more disinhbition signs than Group I (older but with shorter illness duration) ($p = 0.03$) and Group IV (younger and shorter illness duration) ($p = 0.04$). This also suggests that illness duration has a more profound effect on disinhibition signs.

Table 5.15. Post-hoc analysis of demographic characteristics and SNS among patient groups with different age and illness duration

	Gp I vs GpII	Gp I vs Gp III	Gp I vs Gp IV	Gp II vs Gp III	Gp II vs Gp IV	Gp III vs Gp IV
Education level	ns	ns	ns	ns	0.004	0.0002
Intelligence	ns	ns	ns	ns	ns	0.05
Motor coordination	ns	0.03	ns	ns	ns	0.03
Sensory integration	ns	ns	ns	ns	ns	Ns
Disinhibition	0.03	ns	ns	ns	0.04	Ns
Total soft signs score	ns	0.05	ns	ns	ns	0.04

Group I: Age>=38 & Du<=12; Group II: Age<38 & D>12; Group III: Age>=38 & Du>12; Group IV: Age<38 & Du<=12

ANCOVA controlling for education level

In view of the significant differences in education level found among the groups, an ANCOVA controlling for education level was conducted. After controlling for education level there was no main effect on age and illness duration found in motor coordination [$F(3,186) = 2.545$, $p>0.05$], sensory integration [$F(3,170) = 0.458$, $p>0.05$], disinhibition [$F(3,174) = 2.215$, $p>0.05$], and total soft signs score [$F(3,165) = 1.94$, $p>0.05$].

Post-hoc analyses indicated that Group III (older and longer illness duration) exhibited significantly more motor coordination signs than Group IV (younger and short illness duration) ($p = 0.03$), but was not significantly different from Group II (Younger but longer illness duration). This would also support the position that for motor coordination signs illness duration has a more important effect than age *per se*.

Likewise, Group II (younger age with long illness duration) demonstrated significantly more disinhbition signs than Group I (older but with shorter illness duration) ($p = 0.04$) and Group IV (younger and shorter illness duration) ($p = 0.04$). Once again, this suggests that illness duration has a more profound effect.

Section Summary

This section presents further analysis of the effects of age and illness duration. Firstly patients and control groups were divided into subgroups of different ages and SNS scores were compared. After consideration of co-variation with education level, there was no significant different between subgroups of different ages. It was noted in *post hoc* analysis however that, in the patient groups, the extremes of lower age and higher age had less and more SNS respectively. Patients were then grouped

according to illness duration and then compared. There was a significant increase in motor coordination signs associated with illness duration. Finally patients were grouped according to both age and illness duration in to four groups. Although after controlling for education level, there was no overall difference in SNS, post hoc analysis indicated that patient with long illness duration (whether younger or older) had more SNS.

Summary of findings for Chapter 5

There are correlations between SNS, education level and intelligence level. Overall gender effect of SNS is not apparent although there may be a trend difference in motor coordination. There is a gender difference in the pattern of correlation with symptoms. Though there is no unequivocal ethnicity effect for total SNS, there is a suggestion that sensory integration signs might be lower in Chinese subjects. Relationship with symptoms is very modest apart from a relationship with the "thought" domain in negative symptoms amongst female patients. There is an effect of illness duration on the level of SNS which appears to be more important that the effect of age *per se*.

6 SNS and cognitive functions

Introduction

In this chapter the relationship between cognitive function domains and neurological signs is considered. The exploration starts with correlation relationships between SNS and cognitive functions. When relationships between a larger numbers of domains are considered, correlation analysis on its own may be insufficient. This is particularly important when internal correlations exist between these variables. The questions then arise as to the extent to which the correlation between one variable and another is mediated by their mutual correlation with a third variable. Regression analyses were carried out to take into account internal correlation amongst variables.

Cognitive correlates related to age, education, and illness duration

Preliminary correlation analysis was carried out to assess the extent to which cognitive performance were related to variables such as age, illness duration and education level. The sample consisted of 195 patients from Study 1.

After correction for multiple comparisons (Bonferroni method), there were significant correlations between age and sustained attention, verbal performance, verbal fluency, visual reproduction, and Wisconsin Card Sorting Test criterion score (Table 6.1). Significant correlations were also found between education level

sustained attention, verbal performance, verbal fluency, logical memory, and visual reproduction, and perseverative error and category score in Wisconsin Card Sorting Test. These results indicate that similar to SNS, a number of cognitive functions are correlated with age, education level and illness duration. Therefore, in further exploration of the relationship between SNS and cognitive functions, age, education level, and illness duration were controlled for in the partial correlation analysis.

Table 6.1. SNS correlates of age, education level, and neurocognitive functions

	Age	Education level
Attention	-0.29****	0.44****
Logical memory	-0.24****	0.39****
Digit span forward	-0.35****	0.51****
Verbal intelligence	-0.39****	0.66****
Verbal fluency	-0.29****	0.41****
Visual memory	-0.43****	0.52****
WCST perseverative errors	0.21***	-0.29****
WCST category	-0.31****	0.36****

*p<0.05, **p<0.01, ***p<0.005, ****p<0.001

Relationship between SNS and cognitive functions: partial correlation analysis

Correlation analysis of the relationship between neurological signs and cognitive performance was carried out using partial correlation coefficients controlling for age and education level (Table 6.2). Because of the large number of correlation analyses, Multiple comparisons were allowed for by adjusting the significance level to 0.0015 (for 33 comparisons). The results indicate that motor coordination soft signs are related to sustained attention, verbal fluency, verbal and visual memory functions,

verbal intelligence whereas sensory integration signs are primarily related to verbal intelligence. There is however some overlap in these relationships (both motor coordination and sensory integration are related to digit span, verbal intelligence and visual memory). The relationship between disinhibition signs and cognitive functions appeared less prominent.

Table 6.2. Partial correlation coefficients between soft neurological signs and neurocognitive functions (controlling for age and education level)

	Attention	Logical memory	Digit forward span	Inform	Compre	Similarity	Verbal IQ	Verbal fluency	Visual memory	WCST p	WCST c
Motor	-0.3*	-0.17	-0.27*	-0.2	-0.17	-0.18	-0.3*	-0.29*	-0.35*	-0.04	-0.01
Sensory	-0.21	-0.21	-0.35*	-0.41*	-0.33*	-0.3*	-0.44*	-0.26	-0.27*	0.14	-0.22
Disinhbition	-0.15	-0.07	-0.25	-0.15	-0.07	-0.16	-0.22	-0.17	-0.21	-0.03	-0.05

Inform:Information,Compre:Comprehenion,WCST p: WCST perseverative errors, WCST c: WCST categories score. *Statistically significant after adjustment for multiple group comparison (p<0.0015)

Factor analysis of cognitive function and neurological signs:

From another perspective, an exploration of the relationship between cognition and neurological signs was carried out using factor analysis (principal component analysis with varimax rotation). The analysis starts with no prior assumption about the grouping of neurological signs and cognitive function domains. All key domains in both cognitive function as well as SNS are included. Two factors with eigenvalues greater than one were extracted, accounting for 57 percent of the variance (Table 6.3). It is noteworthy that the analysis treated each variable (whether cognitive function or neurological signs) on an equal basis. The result was that cognitive functions loaded

on one factor whilst neurological signs loaded on another factor. This result supports the construct of SNS as reflection of a functional domain that can largely be considered separately from cognitive function domains.

Table 6.3. Factor analysis of soft neurological signs and neurocognitive domains

	Factor 1	Factor 2	Eigenvalues	% of Variance	Cumulative %
VIQ	**0.82**	-0.36			
Logical memory sum	**0.74**	-0.11			
WCST perseverative error	**-0.72**	-0.13			
Visual memory	**0.67**	-0.41			
Verbal fluency	**0.59**	-0.37			
Attention	**0.45**	-0.37	2.86	31.73	31.73
Disinhibition	0.00	**0.82**			
Motor coordination	-0.18	**0.78**			
Sensory integration	-0.31	**0.66**	2.30	25.59	57.32

Principal Component Analysis with Varimax Rotation

Regression analyses

Since domains of cognitive functions, as well as SNS are mutually correlated, regression analysis is carried out to identify the most important features related to a particular domain (the dependent variables). Since there was no prior assumption about the relative status of SNS and cognitive functions (as dependent or independent variables) analysis was carried out in both directions. In the first instance, each SNS domain was treated as dependent variables with cognitive domains as independent variables. In the second analysis, each cognitive domain was treated as dependent variable and the SNS domains were treated as independent

variables.

Soft signs as dependent variables

Significant cognitive contributors to motor coordination signs included sustained attention and visual memory (Table 6.4). Significant contributor to sensory integration signs included only verbal intelligence. Visual memory also contributed to disinhibition signs

Table 6.4. Multiple stepwise regression analyses using each soft neurological signs subscale as dependent variables

		Unstandardized Coefficients		Standardized Coefficients	t-value	p-value	R Square	R Square Change
		B	Std. Error	Beta				
Motor coordination								
Step 1	visual memory	-1.07	0.16	-0.46	-6.525	<0.000005	0.21	0.21
Step 2	visual memory	-0.80	0.19	-0.34	-4.299	0.00003	0.24	0.04
	attention	-1.66	0.58	-0.23	-2.844	0.00503		
Sensory integration								
Step 1	Verbal IQ	-0.75	0.11	-0.48	-6.827	<0.000005	0.23	0.23
Disinhibition								
Step 1	visual memory	-0.45	0.11	-0.32	-4.240	0.00004	0.10	0.10

Soft signs as independent variables

Verbal IQ, sustained attention, logical memory, and visual memory were predicted by both motor and sensory SNS. WCST category was predicted by sensory integration (Table 6.5). However, none of the soft signs predicted WCST perseverative errors.

Table 6.5. Multiple stepwise regression analysis using soft neurological signs as independent variables

		Unstandardized Coefficients		Standardized Coefficients	t-value	p-value	R Square	R Square
		B	Std. Error	Beta				Change
Verbal IQ								
Step 1	Sensory SNS	-0.21	0.03	-0.45	-6.644	<0.000005	0.21	0.21
Step 2	Sensory SNS	-0.15	0.03	-0.32	-4.291	0.00003	0.28	0.07
	Motor SNS	-0.17	0.04	-0.30	-4.070	0.00007		
Attention								
Step 1	Motor SNS	-0.05	0.01	-0.42	-6.010	<0.000005	0.18	0.18
Step 2	Motor SNS	-0.04	0.01	-0.33	-4.252	0.00004	0.21	0.03
Logical memory								
Step 1	Motor SNS	-0.16	0.04	-0.27	-3.644	0.00036	0.07	0.07
Step 2	Motor SNS	-0.12	0.05	-0.20	-2.369	0.01898	0.09	0.02
	Sensory SNS	-0.08	0.04	-0.16	-1.990	0.04826		
Verbal fluency								
Step 1	Motor SNS	-0.66	0.12	-0.39	-5.424	<0.000005	0.15	0.15
Step 2	Motor SNS	-0.48	0.14	-0.28	-3.546	0.00051	0.19	0.04
Visual memory								
Step 1	Motor SNS	-0.19	0.03	-0.46	-6.503	<0.000005	0.21	0.21
Step 2	Motor SNS	-0.15	0.03	-0.37	-4.914	<0.000005	0.25	0.04
WCST category								
Step 1	Sensory SNS	-0.02	0.01	-0.26	-3.525	0.00055	0.07	0.07

Summary of findings for Chapter 6

The analysis of relationship between cognitive function and SNS is complicated by the fact that internal correlation exists between domains within these areas. Analyses from several different perspectives have been carried out to obtain a richer picture.

Regression analyses also support a prominent contribution of verbal intelligence to sensory integration signs. For motor coordination signs, in addition to verbal intelligence, sustained attention and visual memory are significantly related.

7 Longitudinal study in chronic schizophrenic patients

Introduction

This chapter presents a longitudinal study in which a sample of stable chronic schizophrenic patients was studied with respect to SNS and followed up for 3 years and reassessed. The sample consisted of 38 inpatients with chronic schizophrenia; the characteristic of the sample was described in Chapter 4. Data analysis first compared and identified any change in clinical parameters in the sample over the follow-up period. It is important to recall that the mean age for this sample was 47.3 years and the mean illness duration was 25.9 years.

Did clinical parameters remained unchanged at follow-up?

Symptom changes between baseline and year 3 were compared with paired t-tests (Table 7.1). There was a significant reduction of negative symptoms at year 3. Therefore in assessing change in SNS during the follow-up period it is important to determine if it was related to negative symptoms changes.

Table 7.1. Comparison of symptoms between baseline and 3-year follow up in chronic patients

	Baseline		3-year Follow up			
	Mean	SD	Mean	SD	t-value	p-value
Chlorpromazine equivalence (mg/day)	844.61	690.75	828.78	687.55	-0.119	0.9058
Benzhexol (mg/day)	4.22	3.22	5.08	3.11	1.654	0.1069
HENS total	2.51 (1.02)	1.02	1.86	0.77	3.393	0.002
BPRS total	27.68	6.83	28.63	6.21	0.725	0.4733
MADRS total	2.89	3.74	1.74	2.39	1.906	0.0645
Extrapyramidal signs	13.16	13	17.43	14.1	2.012	0.057

HENS: High Royds Negativism Scale; BPRS: Brief Psychiatric Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale

Is there any deterioration in SNS during the follow-up period

Longitudinal comparison between soft neurological signs at year 1 and year 3 was carried out using paired sample analysis (Table 7.2). There was a significant increase in motor coordination, sensory integration, and disinhibiton signs.

Table 7.2. Longitudinal changes in neurological soft signs in chronic patients

	Baseline		3-year Follow up		
	Mean	SD	Mean	SD	p-value
Motor coordination (n = 36)	22.86	28.64	29.84	31.4	0.0321
Sensory integration (n = 25)	14.5	21.25	25.5	22.09	0.0364
Disinhibition (n = 26)	13.46	13.66	28.85	19.29	0.0002

Does the difference remain after controlling for negative symptoms?

Since there was a change in negative symptoms across the follow-up period, within-subject analysis of covariance was carried out to control for this variable. The dependent variables are each of the SNS subscale scores. Difference in HEN score was used as a covariate. Significant increase was present in motor coordination ($F=7.03$, $df=1,32$; $p=0.012$) and disinhibiton signs ($F=13.52$, $df=1,23$; $p=0.001$), trend increase was observed in sensory integration signs ($F=3.53$, $df=1,22$; $0=0.074$).

Summary of findings for Chapter 7

Significant increase in motor coordination, sensory integration and disinhibition signs were observed in a chronic patient sample in a longitudinal study of 3-year follow-up period. The changes in motor coordination and disinhibition signs are still significant after taking into account changes in negative symptoms.

This is a sample of patients without clinical relapse or substantial changes in medication, and there was a decrease in negative symptom score in the follow-up period. The data indicate that an increase in SNS was detected in spite of an improvement in negative symptoms. Either aging or degenerative processes may operate and they appeared to act independently of mechanisms that mediate negative symptoms.

8 Longitudinal study in first episode psychosis

Introduction

In this Chapter data addressing motor soft neurological signs in the early stages of schizophrenia and related psychosis are examined in more detail. In particular the assessment of medication-naïve patients and the longitudinal follow-up design (4-monthly for 2 years) enable the data to address a number of research questions:

1. Are motor SNS increased in first episode patients?

2. Are motor SNS in first episode patients comparable to chronic patients?

3. Is there progression in the level of soft neurological signs in the first two years of the illness?

4. Does motor SNS improve after resolution of the psychotic episode?

5. Do soft neurological signs deteriorate after a relapse?

6. Is there a phase-specific relationship between motor SNS and cognitive function?

7. Is there a phase-specific relationship between motor SNS, clinical features, and cognitive function?

The data presented in this chapter is obtained in the context of a larger study investigating the longitudinal changes in cognitive function following first episode psychosis. The sample is a set of consecutively diagnosed patients from a defined catchment area within Hong Kong (Hong Kong island and offshore islands). The patients are assessed at the point of first contact (initial assessment), and then after the resolution of the first psychotic episode (clinical stabilization). The mean duration between the two time points is 42.5 days (SD = 37). Subsequently assessments were carried out at regular intervals (4 monthly) for a period of 2 years. Basic characteristics of the sample have been presented in Chapter 4.

Because of limitations in the length of the assessment session, it was not feasible to incorporate the full CNI into the study. An abridged soft signs assessment consisting of the motor coordination subscale was adopted. This choice was based on the earlier observation that among the soft signs, sensory integration signs were more strongly associated with verbal cognitive performance (see Chapter 6 for details), which are already addressed by other cognitive function tests (WAIS information, WMS logical memory, and semantic fluency). Extra-pyramidal signs and dyskinesia were assessed by independent rating scales. The data that will be considered consists of signs in the motor coordination subscale.

Sample characteristics

The clinical and neurocognitive profile of the sample at initial presentation are presented in Table 8.1.

Table 8.1. Clinical and cognitive profile of first episode patients

	Mean	SD
Clinical Profiles		
PANSS positive	20.49	6.12
PANSS negative	16.88	7.52
PANSS general pathology	34.41	12.30
PANSS total score	76.51	22.93
HEN	1.11	0.87
MADRS	9.29	12.53
AIMS	0.12	0.76
SIMS	0.63	1.98
BARNES	0.24	0.87
Nerocognitive function		
Logical memory (immediate)	36.51	17.79
Logical memory (delay)	29.07	17.59
Visual reproduction (immediate)	18.38	4.57
Visual reproduction (delay)	16.47	5.79
Information subscale	13.54	4.95
Forward digit span	11.07	2.25
Verbal fluency	16.15	5.04
WCST perseverative errror	8.22	9.26
WCST category score	3.75	2.00

PANSS: Positive and Negative Symptoms Scale; HEN: High Royds Evaluation of Negativity
MADRS: Montgomery and Asberg Depression Rating Scale; CAL: Calgary Depression Scale
YBSEV: Yale-Brown Obsessive Compulsive Scale; AIMS: Abnormal Involuntary Movement Scale; SIMS: Simpson-Angus Movement Scale; BARNES: Barnes Akathisia Scale

Are motor soft signs increased in a first episode psychosis?

To address this question motor soft signs scores from patients were compared with a control group matched for age and education level (Table 8.2).

Table 8.2. Demographic data in first episode patients and healthy control subjects

	First episode patients (n = 68)		Healthy controls (n = 68)	
	Mean	SD	Mean	SD
Age	32.9	9.5	32.0	8.4
Education level (years)	10.2	3	9.4	2.6
Gender (M:F)	30 : 38		22:46	

The results are shown in the Table 8.3. Significant differences were found between the two groups with a moderate effects size. Non-parametric analysis (Mann-Whitney U-test) also confirmed a significant increase in motor soft sign in patients. The result thus supports the notion that motor soft signs are increased in first-episode schizophrenia.

Table 8.3. Comparison of motor SNS between first episode patients and healthy control subjects

	First episode patients (n = 68)	Healthy controls (n = 68)	t-value/ z-statistics	df	p-value	effect size
Parametric analysis Mean (SD)	19.28 (22.19)	9.48 (14.78)	3.031	134	0.0029	0.53
Non parametric analysis mean rank	77.71	59.29	0.292	--	0.003	--

Are motor soft signs increased in medication-naïve patients

Since only around 50% of the 68 initial assessments were conducted in a medication-naïve state (the rest were carried out shortly after initiation of antipsychotics therapy),

the subset of medication-naive patients (n=34) was further examined. Table 8.4 summarizes the characteristics of medication-naïve patients as compared to those who had been started on medication for days. No significant differences was found among the groups in terms of age, education level and gender proportion.

Table 8.4. Comparison of demographic variables among recently-medicated patients, medication-naïve patients and healthy control subjects

	Medication-naïve patients (n = 34)		Recently-medicated patients (n = 34)		Healthy controls (n = 68)	
	Mean	SD	Mean	SD	Mean	SD
Age	32.7	9.2	33.1	9.9	32	8.4
Education level (years)	9.9	3	10.4	2.9	9.4	2.6
Gender (M:F)	15:19		15:19		22:46	

As seen in Table 8.5, both parametric and non-parametric analyses indicated a significant increase of motor soft signs in medication-naïve first episode patients.

Table 8.5. Comparison of motor SNS between medication-naive patients and healthy control subjects

	Medication-naïve patients (n = 34)	Healthy Controls (n = 68)	t-value/ z-statistics	df	p-value	effect size
Parametric analysis Mean (SD)	18.63 (22.84)	9.48 (14.78)	2.441	100	0.0164	0.18
Non-parametric analysis mean rank	60.09	47.21	2.257	--	0.024	--

When comparison was made between medication-naïve and medicated patients, no significant differences were found between the two groups in motor soft signs (Table

8.6). This would support that there was no immediate change in motor soft signs following initiation of treatment.

Table 8.6. Comparison of motor SNS between recently-medicated and medication-naïve patients

	Medication-naïve patients (n = 34)	Recently-medicated-patients (n= 34)	t-value/ z-statistics	df	p-value	effect size
Parametric analysis Mean (SD)	18.63 (22.84)	19.93 (21.85)	0.24	66	0.24	0.06
Non-parametric analysis) mean rank	33.2	35.4	0.388	--	0.698	--

Comparison between first-episode and chronic patients

To address the question of whether the extent of soft signs found in first episode patients is comparable to that found in chronic patients; a comparison was made between the first episode sample and an age/education-matched sample of chronic schizophrenic patients drawn from Study 1.

Table 8.7. Comparison of demographics between first episode patients and chronic patients

	First episode Patients (n = 68)		Chronic patients (n = 100)					
	Mean	SD	Mean	SD	t-value /Chi-sq	df	p-value	Effect size
Current age	32.91	9.51	32.23	7.01	0.535	166	0.5934	0.08
Education level (years)	10.16	2.96	9.37	2.72	1.787	166	0.0757	0.28
Gender (M:F)	30:38	--	62:38	--	5.224	1	0.027	--

Demographic information of the comparison sample is presented in Table 8.7. The

mean illness duration of the chronic patients was 10.4 years (s.d. 7.5). No significant difference was found in motor signs between first episode patients and patients with chronic schizophrenia. In fact the mean SNS scores were lower in chronic patients compared with patients with first episode psychosis (Table 8.8).

Table 8.8. Comparison of motor SNS between first episode patients and chronic patients

	First episode patients (n = 68)		Chronic patients (n = 100)		t-value/z statistics	df	p-value	effect size
Parametric analysis Mean (SD)	19.28	22.19	13.56	18.66	1.9	164	0.06	0.28
Non-parametric analysis Mean rank	140.25	--	128.05	--	1.92	--	0.06	--

Since the level of soft neurological sign in first-episode patients might have been enhanced by the psychotic state, a further comparison between the chronic patients and first episode patients *after clinical stabilization* was also carried out (Table 8.9).

Table 8.9. Comparison of motor SNS between first episode patients after clinical stabilization and chronic patients

	Stabilized first episode patients (n = 68)		Chronic patients (n = 100)		t-value/ z-statistics	df	p-value	Effect size
Parametric analysis Mean SD	15.52	21.9	13.56	18.66	0.625	164	0.625	0.1
Non-parametric analysis Mean rank	86.28	--	83.29	--	0.42	--	0.675	--

It can be seen that when assessed soon after clinical stabilization, the level of motor soft signs in first episode patient is comparable to that seen in chronic patients. This observation suggested that there is probably no substantial deterioration in soft neurological signs from first episode to chronic schizophrenia (average illness duration 10 years).

Comparison between first presentation and clinical stabilization

To address the question of whether the psychotic state itself substantially increases the presence of motor soft signs, a within-subject comparison was carried out between scores at initial presentation and scores after clinical stabilization. No significant difference was found (Table 8.10). Non-parametric Wilcoxon signed rank test showed similar insignificant findings. The result suggests that the increase in motor soft sign is not merely secondary to acute psychotic symptoms.

Table 8.10. Comparison of motor SNS between first presentation and clinical stabilization

	First presentation		Clinical stabilization		t-value/ z-statistics	df	p-value	Effect size
Parametric analysis Mean/ SD	19.28	22.19	15.52	21.90	1.29	67	0.202	0.17

Is there a longitudinal decline in SNS in the two years following a first episode psychosis?

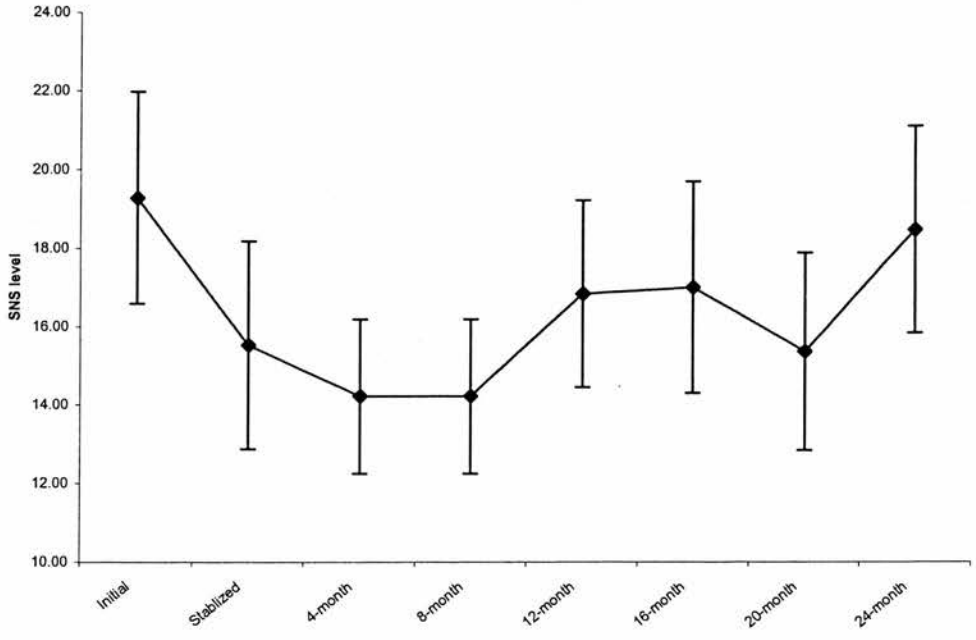
The mean level of motor soft neurological signs was considered across the different time points in the first 2 years (Figure 8.1). A linear regression analysis showed that

the slope of the regression line of motor soft signs scores in relation to time was not significantly different from zero thus suggesting that there was no overall increase in the level of signs across time.

Table 8.11. Changes of motor SNS across a 2-year time period

	First presentation		Clinical stabilization		4-month		8-month		12-month		16-month		20-month		24-month	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Motor SNS	19.3	22.2	15.5	21.9	14.2	16.3	14.2	16.3	16.8	19.7	17.0	22.3	15.3	20.8	18.5	21.7

Figure 8.1: Changes of motor soft signs in the 2 years following a first episode psychosis



The data suggest that in the early course of psychosis, motor soft signs remain at an increased level and did not reveal evidence of decline over the first two years.

Do SNS deteriorate during a relapse?

For the 16 patients who experienced a relapse (defined as a deterioration in positive symptoms leading to re-hospitalization), motor soft signs were examined during acute relapse and after treatment of the relapse. Table 8.11 shows that no significant differences were found between admission and discharge during a relapse (defined by re-hospitalization). This was also confirmed with non-parametric Mann-Whitney U-test. This comparison has to be interpreted as preliminary in view of the relatively small sample size for those patients in whom a relapse occurred. It is noted that the mean motor soft signs score in the group of patient who relapse appeared to be lower that the scores for the entire group of patients at the end of the first episode.

Table 8.12. Comparison of motor SNS between acute relapse and after treatment of the relapse

	Acute relapse (n = 16)		After treatment of relapse (n = 16)		t-value/ z-statistics	df	p-value	Effect size
Parametric analysis Mean / SD	11.81	19.65	6.94	17.15	1.023	15	0.323	0.26
Non-parametric analysis Mean rank	4.75	--	4.42	--	1.204	--	0.229	--

Clinical and demographic correlates of motor soft signs

At initial presentation

Onset age and education level were significantly correlated with motor soft signs. A higher onset age is modestly associated with increased level of motor soft signs ($r=0.29$, $p=0.02$). A higher level of education is associated with a decreased level of soft neurological signs ($r=0.47$, $p=0.0001$). DUP was not found to be associated with the level of soft neurological signs. Notably, the association with age at the beginning of psychosis suggests that onset age contributes to the level of SNS independent of illness duration.

There was no significant correlation between the levels of soft neurological signs and the level of positive and negative symptoms, affective and obsessive compulsive symptoms, as well as measures of extrapyramidal signs.

Clinical stabilization

After clinical stabilization, the level of soft signs was found to be modestly positively correlated with negative symptoms scores ($r=0.26$, $p=0.03$). In addition there was also a correlation with the level of extrapyramidal signs ($r=0.3$, $p=0.01$). The relationship with negative symptoms thus became more apparent at clinical stabilization. The relationship with extrapyramidal signs raises the possibility that side effects to antipsychotic medication might interact with the expression of soft

neurological signs.

The significant relationship between motor SNS and negative symptoms disappears after controlling for extrapyramidal effects. This indicates that the relationship with negative symptoms could be mediated by extrapyramidal effects. It is important to note that extrapyramidal signs though often attributed to antipsychotic medication, may also reflect illness-related features that are present before the onset of medication treatment, and in fact may constitute target features in their own right.

The contribution of medication side effects towards manifestation of SNS is a difficult issue to resolve. The presence of increased level of SNS in medication-naïve patients suggests that medication effects could not entirely account for the expression of SNS. However, it is difficult to rule out the possibility that after treatment with antipsychotic medications, part of the SNS expression might be mediated by medication. While most of the time extrapyramidal side effects are controlled by dosage adjustments and anticholinergic medications, extrapyramidal signs were found to be modestly correlated with SNS after antipsychotic treatment was initiated. It is intriguing, however that the overall level of SNS did not increase (actually there was a trend decrease). These observations suggest that other state variables, such as the presence of psychosis, might also interact with manifestations of SNS in a dynamic and stage-specific manner.

SNS correlation with cognitive function performances in first episode psychosis

The relationship between motor soft signs and cognitive functions was explored in a series of correlation analysis using data from different time points in the course of early psychosis (Table 8.13).

On admission, significant inverse correlation was found between motor soft signs and visual reproduction (delayed score) as well as verbal fluency.

After the stabilization of the psychotic symptoms, motor soft signs were significantly correlated with immediate logical memory recall, immediate and delayed visual reproduction, digit span, verbal fluency, and category score of WCST. Similar trends and pattern were observed between motor SNS and the neurocognitive performances at 1 year and 2 years.

Table 8.13. Correlation between motor SNS and neurocognitive functions

	LM (immed)	LM (delay)	Vis mem (immed)	Vis mem (delay)	Information	Digit forward	VF	WCST per	WCST Cat
First presentation	-0.17	-0.16	-0.23	-0.29	-0.23	-0.19	-0.25	0.05	-0.18
Clinical stabilization	-0.30	-0.23	-0.59*	-0.47*	-0.21	-0.33	-0.32	0.12	-0.25
Year 1	-0.32	-0.23	-0.45*	-0.33	-0.24	-0.46*	-0.25	0.24	-0.42*
Year 2	-0.27	-0.19	-0.41*	-0.35	-0.27	-0.37	-0.44*	0.36	-0.28

LM: logical memory; Vis mem: visual reproduction; VF: Verbal fluency; WCST per: WCST perseverative error; WCST cat: WCST category
*significant after adjusting multiple group comparison, i.e. $p<0.0005$

A similar picture was observed after partialling out the effects of education level, as well as the information subscale of the WAIS (a measure of verbal intelligence) (Table 8.13). Thus the correlational relationships between motor soft sign changed with time in the course of early psychosis. Initially a more restricted range of correlation appeared. After clinical stabilization a wider range of cognitive functions were related to motor soft signs. This pattern persisted in subsequent comparison at year 1 and year 2. Motor soft signs were related to both prefrontal functions such as WCST score and verbal fluency scores. There was also a relationship with memory functions (visual reproduction and digit spans). These relationships survived the partialling out of education level and general intelligence effects.

Table 8.14. Partial correlation coefficients between motor SNS scores and cognitive variables (controlling for education level and intelligence estimate)

	LM (immed)	LM (delay)	Vis mem (immed)	Vis mem (delay)	Digit forward	Verbal fluency	WCST per	WCST cat
First presentation	-0.15	-0.15	-0.1	-0.25	-0.19	-0.24	0.03	-0.07
Clinical stablization	-0.24	-0.15	-0.55*	-0.41	-0.23	-0.27	0.05	-0.16
Year 1	-0.30	-0.17	-0.45*	-0.34	-0.42*	-0.16	0.17	-0.38
Year 2	-0.23	-0.15	-0.37	-0.3	-0.29	-0.35	0.32	-0.23

LM: logical memory; Vis mem: visual reproduction; VF: Verbal fluency; WCST per: WCST perseverative error; WCST cat: WCST category
*significant after adjusting multiple group comparison, i.e. $p<0.0005$

Regression analysis

Since there may be internal correlation between different cognitive functions,

regression analyses was carried out at each time point to evaluate the relative contribution of different cognitive variables in their association with motor soft signs.

Table 8.14 shows that at initial presentation in the medication-naïve state, education level was the only contributor of motor coordination signs. After clinical stabilization, visual reproduction performance became the most important correlates of motor soft signs, followed by age of onset. At the end of year one, visual reproduction, forward digit span, and WCST category score were the most important correlates. At year 2, age at onset, visual reproduction score and verbal fluency score were the most important predictors of motor soft signs levels.

To summarize, education level and onset age seemed to be the crucial correlates of motor soft signs at first presentation and clinical stabilization of psychosis. From clinical stabilization onwards up to two years follow-up, visual reproduction score is the most important predictor of motor soft signs. Forward digit span and WCST category score were also significant predictors at the end of year 1.

Table 8.15. Multiple stepwise regression analysis on motor SNS

		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R Square	R Square
		B	Std. Error	Beta				Change
Initial presentation								
Step 1	education	-3.63	0.82	-0.49	-4.435	0.00004	0.24	0.24
Clinical stable								
Step 1	Visual reproduction (immediate)	-3.60	0.62	-0.58	-5.775	<0.000005	0.34	0.34
Step 2	Visual reproduction (immediate)	-3.04	0.62	-0.49	-4.905	0.00001	0.42	0.08
	onset age	0.67	0.23	0.29	2.928	0.00473		
Year 1								
Step 1	Digit forward	-4.62	1.10	-0.46	-4.207	<0.000005	0.21	0.21
Step 2	Digit forward	-3.27	1.17	-0.33	-2.803	0.00666	0.29	0.08
	Visual reproduction (immediate)	-1.64	0.62	-0.31	-2.648	0.01014		
Step 3	Digit forward	-2.66	1.17	-0.26	-2.270	0.02657	0.34	0.05
	Visual reproduction (immediate)	-1.34	0.62	-0.25	-2.166	0.03403		
	WCST category	-2.67	1.24	-0.24	-2.149	0.03546		
Year 2								
Step 1	Onset age	1.10	0.25	0.48	4.40	0.048	0.23	
Step 2	Onset age	0.94	0.24	0.41	4.03	0.0001	0.36	0.13
	Visual Reproduction (immediate)	-2.31	0.66	-0.36	-3.5	0.0008		
Step 3	Onset age	0.84	0.22	0.37	3.73	0.004	0.44	0.08
	Visual Reproduction (immediate)	-1.93	0.63	-0.3	-3.05	0.003		
	Verbal Fluency	-1.39	0.46	-0.3	-3.04	0.003		

Summary of findings for Chapter 8

Motor SNS are increased in medication-naïve first episode psychosis patients. The level of motor signs seen in first episode patients is not significantly different from those seen in chronic patients. There is a suggestion that the mean level of motor signs is slightly reduced following clinical stabilization of the first episode illness. At initial presentation the level of SNS is related to education level and onset age. DUP was not related to the level of motor soft signs, suggesting that soft signs did not reflect any processes that may progress during the DUP. SNS was not related to symptoms and extrapyramidal signs at presentation. However, the pattern of SNS correlates changed after antipsychotic therapy had brought about clinical stabilization. SNS were modestly correlated with both negative symptoms and with extrapyramidal signs at this stage. The correlation with negative symptoms appeared to be mediated by extrapyramidal signs. This suggests that although the overall total score change was insignificant; there may be more subtle changes in SNS expression. Further analysis of SNS in the 16 patients who experienced a relapse during the study period did not suggest a change in motor SNS before or during a relapse, although this conclusion is limited by the relatively small number of patients who had a relapse during the study period. The pattern of correlation between SNS and cognitive function also changes with treatment, at initial presentation SNS was only modestly related to a small number of cognitive functions (visual reproduction and verbal fluency). Following treatment and stabilization SNS become associated with a broad range of cognitive function (digit span, WCST, logical memory, visual

reproduction and verbal fluency). This pattern of correlation then persisted in the subsequent assessment during the 2-year follow-up period. Verbal fluency and visual reproduction remained as the strongest predictors for SNS during the period. Interestingly visual reproduction was also found to be an important correlate of SNS in the cross-sectional study (Study 1). Longitudinally there was no overall change in SNS level in the 2-year follow-up period.

9 Discussion

Overall summary of findings

This dissertation describes a series of studies addressing manifestations of soft neurological signs in schizophrenia. In study 1 a larger cross-sectional sample of schizophrenic patients were studied with a corresponding healthy control group. The study firstly addressed relationship between SNS, education level and intelligence level. The data confirms a robust relationship between SNS and education level as well as intelligence. This relationship was identified not only in the patient sample but also amongst healthy control subjects. The relationship between SNS, age and illness duration was further addressed by subgroup comparison with analyses of variance. The analyses suggest that longer illness duration is related to the presence of increased motor SNS, there is also a suggestion of a relationship with age but that was confounded by education level differences in the samples.

Further analysis allowed a more detailed exploration of the relationship between SNS, clinical picture, cognitive function and other neurological signs. This revealed that there is little relationship between SNS and positive symptoms, however a gender-specific association between SNS and negative symptom ("thought" domain) emerged in female patients. Apart from revealing extensive relationship between cognitive function domains and SNS, the data suggest a differential relationship between motor SNS and certain cognitive functions (such as sustained attention and visual memory), as well as a relationship between sensory integration signs and a

broader range of cognitive functions.

A comparison between healthy control group in Chinese subjects and Caucasian subjects also provided data addressing the ethnic variation of SNS. The data suggest that there is no significant variation in overall SNS between Chinese and Caucasian patients, however there is a suggestion that the subgroup of sensory integration signs might be less prevalent in Chinese subjects.

Cross-sectional data was complemented by two sets of longitudinal data. A 3-year longitudinal study of SNS in stable chronic schizophrenic patients provided evidence supportive of the possibility of deterioration in soft neurological signs for at least a subset of patients in late middle age with chronic illness. The 2-years study of motor SNS in first-episode patients revealed that SNS was already increased in the first episode psychosis before treatment. The level of SNS appeared to remain stable for the first 2 years of illness. However the pattern of correlates changed with time, suggesting that while the overall SNS level was stable, the nature and constituent processes might be evolving. These findings, their limitations as well as their relationship with existing findings are further discussed in the following sections.

Intelligence and education level

The current data suggests that SNS is correlated with intelligence and education level not only in patients but also in healthy control subjects. This relationship was seen in both the Chinese and the Caucasian control samples. The current results also confirm

that amongst schizophrenic patients both intelligence and education level are associated with SNS. Subscale analysis revealed that correlation was found in all the three subscales (motor coordination, sensory integration and disinhibition) of the CNI.

In the light of increasing recognition that schizophrenia has a neurodevelopmental component, intelligence and education level probably should not be viewed as mere "demographic" variables that constitute simple antecedent risks for the disorder. Instead, similar to SNS, intelligence and education level could be construed as downstream consequences of earlier developmental events. Thus in pondering their relationship, it may be more appropriate to consider both SNS and intelligence level as reflections of developmental features that indicate a neurointegrative dysfunction. In this perspective, an important question is the extent to which SNS and intelligence are independent in the expression of the underlying developmental dysfunction. It has been noted previously that for affective symptoms in adolescence, SNS appear to relate to psychopathology independent of intelligence(143). It is not clear whether the same applies to schizophrenia. It is recognized that the prevalence of schizophrenia is about three times higher in subjects with learning disability (144). The exact explanation for this is unclear, but one of the hypotheses is that overlapping underlying features are involved in both schizophrenia and learning disability. The relationship between intellectual impairment and schizophrenia has also been explored in a study by Doody et al (97), in which subjects with either mild learning disability, or schizophrenia, and those with both of the conditions were

compared. The study found that SNS are higher in the co-morbid group and in mild learning disability group than in the schizophrenia alone group. The authors discussed various ways in which the manifestation of SNS in the two conditions could be related. This includes sharing of common aetiological factors, epiphenomenon (mental limitations predisposes to psychotic symptoms); as well as interaction between the two factors to produce schizophrenia with poor prognosis.

Gender effects

In most previous studies, significant gender difference in soft neurological signs was not found. No significant gender difference was found in overall level of SNS even after taking into consideration age and intelligence. The lack of gender difference in SNS expression in schizophrenia is interesting in the context of reports of gender differences in several other aspects of schizophrenia, including age of onset (145;146), cognitive profile (147;148), symptoms, treatment response and outcome (149-152). Lack of gender effect in SNS would suggest that these aspects of the disorder are less likely to be involved in SNS expression. There is of course a possibility of measurement and sampling variations. There is a need for more detailed examination of this issue in the same sample of patients where gender-sensitive and gender-insensitive variables are examined and compared. However though the overall level of SNS was not different, the correlation between SNS and symptoms appear to be gender-specific (see below).

Correlations with Symptoms

In contrast to previous studies, strong correlations between symptom domains and SNS were not found in the entire sample. However it was found that in particular amongst female patients, negative symptom sub-domain "thought' was specifically associated with SNS. No such association was found amongst male patients. This finding suggests there might be gender variations in the pattern of symptom correlates amongst neurological signs. The finding of gender difference in symptom correlates of SNS is in line with Malla et al (53) who found that negative symptoms correlated with different SNS factors in male and female patients. This potential gender-related pattern of correlation might underlie inconsistencies in some previous findings as these studies consisted of samples with different gender ratios.

The pattern of symptom correlation in first episode patients is also noteworthy. It is important to note at the initial assessment, in the medication-naïve state, SNS were not strongly correlated with symptoms. However after clinical stabilization motor SNS were found to be correlated with negative symptoms as well as extrapyramidal signs. Partial correlation analysis suggests that the relationship with negative symptoms may be mediated through extrapyramidal signs. This raises the important possibility that (though definitely not the sole explanation for SNS) antipsychotic medication may play a role in SNS in mediating its relationship with negative symptoms. The relationship is further complicated by the recognition that extrapyramidal signs are themselves of heterogeneous origin. In addition to

extrapyramidal signs attributable to medication, spontaneous extrapyramidal signs have been observed in medication-naive patients (153-155). The extent to which these spontaneous extrapyramidal signs are related to SNS is an interesting empirical question. Further studies should be carried out to investigate SNS expression in patients with and without spontaneous extrapyramidal signs, in order to delineate the extent to which each of these is an independent feature of the illness.

Ethnicity effects

Buchanan and Heinrich reported that healthy African Americans have an increased level of soft signs compared with Caucasians. The increase was particularly found in the sensory integration subscale (31). In the current study it was found that there was no significant difference in the total SNS score between Chinese and Caucasian healthy subjects. However, there was a trend for Chinese subjects to have lower scores in the sensory integration subscale. Taken together, this tentatively suggests that among the subscales in SNS, sensory integration might be more vulnerable to ethnic variations. The nature of such variations is unknown. It appears that the assessment and the rating processes are less likely to be sources of variation, as both the linguistic and the conceptual demands involved in SNS evaluation are relatively light, and it is possible to achieve good interrater reliability irrespective of the ethnic origin of the subjects and the raters. A more likely source for ethnic variations in SNS could be of a biological rather than cultural nature. Studies of SNS amongst healthy subjects in different ethnic groups are important for addressing this issue. In

this context it is interesting to note that Gureje (65) speculated that increased SNS in the Nigerian control subjects might relate to the level of obstetric care. These issues require further examination.

An important methodological issue needs to be addressed in future cross-ethnic comparison of SNS, since SNS expression is confounded by intelligence level, study design would have to include measurement of intelligence level. The cross-ethnic comparability of intelligence level estimation (156) will be a difficult issue that studies will have to address.

Effects of Age

In the context of previous inconsistent findings on the relationship between age and SNS, the current study found a linear trend for SNS to increase with age. However the effect became non-significant after covariance analysis controlling for education level. This highlights the possibility that different approaches to address potential confounding variables could have contributed to the inconsistencies in previous findings. A further confound is illness duration, which inevitably confounds age in a cross-sectional study. Importantly, data from the first episode study can contribute towards addressing this issue. By comparing between patients at a similar stage of their illness (first illness episode) effect of age *per se* should be more discernable. It was also found that at first presentation, SNS is positively correlated with age. At this stage SNS is also correlated with age of onset of psychosis but not with duration of untreated psychosis. This observation did not support the suggestion that during

untreated psychosis, ongoing neurological damage (as reflected in SNS) is incurred. Whether there is evidence for neural damage during untreated psychosis is still a contentious issue (157;158). The relationship between SNS and age suggested that normal aging process throughout the lifespan is related to the manifestation of SNS. This is further supported by the finding of a correlation between SNS and age in the healthy control sample.

Illness duration

Data addressing the relationship between SNS and illness duration is conflicting. In Kolakowska's study (85), subjects with SNS were found to have longer illness duration than those without, however when stratified into smaller groups according to illness duration, the proportion of those with SNS was not significantly different. In Flashman et al (95), patients with SNS had a longer illness duration (younger age of onset and same current age). Cuesta et al. (88;89) also found that frontal signs were related to duration of illness. On the other hand, Flyckt et al (111) compared motor tests (including SNS) between first episode psychotic patients and chronic patients and found no significant difference. In the current sample it was found that there was a linear trend for SNS to increase with illness duration. The effect appears to be particularly prominent for the motor coordination subgroup of signs.

The relationship between SNS, age and illness duration is an important issue. Although SNS is known to be present in high-risk subjects and first episode patients, it is important to ascertain whether SNS also progresses with age and illness duration.

This issue is important in clarifying whether SNS, as a target feature, represent those factors only affected by the neurodevelopmental aspect of the disorder, or whether it is also vulnerable to putative progressive processes in the disorder. In addition, it is important to distinguish between changes in SNS associated with illness progression from effects of normal aging. Current analyses suggest that there is an increase in SNS with both age and illness duration.

It is difficult however, to distinguish whether the effect of age or the effect of illness duration is the more important. In this regard, one particular limitation is that in a cross-sectional study, age is usually correlated with illness duration. Further subgroup analysis between patients with higher and lower age, and illness duration, respectively suggests that the effect of illness duration probably plays a more important role in SNS.

Longitudinal studies are required to definitively resolve some of these issues. So far few longitudinal studies have been carried out. Smith et al (159) demonstrated that SNS for a sample of middle age chronic patients SNS are largely stable.

In the longitudinal data addressing a sample of stable and older chronic patients there are some suggestions of progression in SNS. This confirms the trends observed in the larger cross sectional studies. The evidence suggests that at least for a subset of patients with longer illness duration and older mean age, SNS appear to run a progressive course.

Longitudinal studies with a larger sample of chronic patients in their forties or fifties, and a longer follow-up period will be required to definitively resolve the question of whether there is longitudinal progression of SNS at specific stages of the illness, particularly when the patients are approaching old age. It is recognized that cognitive deterioration could occur in schizophrenic patients as they approach late life (160-162). The nature of such decline is still unclear as they are not accompanied by recognizable histopathological changes commonly associated with cognitive deficits (such as those associated with Alzheimer disease) . It has been suggested that the decline represents an interaction between mild degenerative changes and diminished cognitive reserve in schizophrenia (163). The deterioration of SNS in this sample could be related to an early manifestation of such processes.

From the first episode study, it was observed that SNS are already increased in the first psychotic episode. In addition, the level of SNS appeared to be stable for the next two years. The level of SNS did not correlate with the length of the DUP. These findings, together with previous demonstrations of increased SNS in high-risk individuals, would argue that at least for the early phase of the illness, SNS appears to represent a stable target feature. This conclusion is however somewhat complicated by the finding that although the level of SNS remained stable, the clinical correlates appear to change in the early course of the illness.

Relationship with cognitive function

There are only a small number of studies investigating the relationship between

cognitive function and SNS. The exploration of this relationship is important as it addresses the question of the extent of overlap between SNS and various cognitive impairments, and thus their independent values as target features in schizophrenia. Although the overall relationship between SNS and cognitive function appears robust, the detailed pattern of correlation between individual domains within SNS and cognition is so far largely inconsistent. The few studies conducted so far have adopted different designs and included different sets of cognitive assessments. One of the key debates was whether SNS relates broadly to most cognitive functions, or whether SNS relates to specific domains in cognitive functions (such as executive functions). Preliminary findings tend to support overall involvement with a broad range of cognitive functions. However within this context some degree of specificity still remains as a possibility. This question is further complicated by internal correlations between different measures of cognitive functions. One noteworthy observation in the current studies is that visual memory appears to have a particularly robust relationship with motor SNS. This relationship was found independently in both the cross-sectional study, and in the longitudinal study of first episode patients. Since visual reproduction performance involve a number of component processes, it would be important in future studies to attempt to identify which of the process are particularly involved in mediating motor SNS.

Methodological Issues

Blindness of ratings

As in other studies involving SNS, soft signs assessment in the current studies was not conducted blind with respect to the subject group (patients and controls, and patients in different assessment time points). In addition, assessment of SNS was carried out by the same rater involved in cognitive testing. Separate raters were involved in clinical ratings (including side effects ratings in study 4). The lack of blindness in some comparisons opened the possibility for observer bias e.g. where patient vs control comparison was concerned. Certain analyses in studies 1, 2 and 4 were potentially vulnerable to this effect. However, the highly structured assessment procedure with operationalized rating guide offers some protection against subjective bias. In other comparisons, for instance, the assessment of soft signs and symptom were carried out by different raters independently and could be consider blind with respect to one another. The relationships between soft signs and cognitive function were assessed by the same rater and were therefore not blind. The possibility of bias with regards to cognitive function was limited as there is no obvious prior expectation of specific relationship between the areas. In addition, the assessment of cognitive function was highly structured and independent on rater judgement, and for many cognitive assessments the final scores were not apparent until after subsequent *en block* data processing. Therefore results were not immediately available to influence the examination in the same session. In longitudinal studies 3 and 4, though the raters were aware of the assessment time points, they were blind to the previous

score of the same subjects. With regards to the comparison between normal controls and patients, the issue of lack blindness is inherent to the nature of the study. It would have been extremely difficult to arrange for control subjects and patients to be assessed in a setting and in such a way as to effectively prevent the examiner from getting an idea about their group identity. Notwithstanding the structured assessment and rating, in the comparison between normal control and patients, the possibility of bias did exist and appropriate caution in the interpretation of the findings should be made.

The potential contribution of antipsychotic medication in SNS expression

The presence of increased SNS in individuals at high risk for psychosis suggests that SNS expression is not entirely secondary to antipsychotic medication. However the potential role of antipsychotic medication after the onset of treatment is a complex area. In the past, investigators explored this question using mainly two approaches, in the first approach, linear correlations were sought between SNS and medication dosage as well as side effects. In the second approach, SNS levels were monitored as patients switched from conventional anti-psychotics to atypical anti-psychotics (with the assumption that atypical anti-psychotics were less liable to produce motor side effects). In both of these approaches the detection of a relationship between SNS and medication depended on there being a linear relationship (i.e. the level of SNS is expected to be related to the type or quantity of medication and motor side effects).

Most previous investigators concluded that the level of SNS was not directly related to antipsychotic medication. Evidence came from the lack of association between SNS and medication dosage or between SNS and extrapyramidal signs(46). Moreover, it was also found that the level of SNS did not change when conventional antipsychotics were replaced by atypical antipsychotics(115). In contrast to previous findings, in study 4 in the current data set, an emergent correlation was identified between soft signs and extrapyramidal signs following treatment of the first psychotic episode. In study 3, extrapyramidal side effects also increased alongside with SNS in the longitudinal follow-up period. However, in the cross-sectional study (study 1), no correlation was detected between SNS and extrapyramidal side effects. These findings echoed the small number of studies which observed a relationship between SNS and extrapyramidal signs(106). In summary, the current data set provided some suggestion that a relationship between SNS and extrapyramidal signs may exist. This relationship may be difficult to detect based on linearly correlations, which might become apparent only at certain stages in the illness. However the lack of a detectable linear relationship does not exclude more subtle relationships between antipsychotic medication and SNS. For instance, a threshold-based relationship may exist between antipsychotic medication and SNS expression whereby only the presence of antipsychotic medication above a certain threshold level has an impact on SNS expression. Such a possibility is reinforced when the complexity inherent in the dimensions of SNS is considered. For instance, in a previous study of the component dimension of SNS, it was identified that at least two dissociable

dimensions exist, of which one corresponded to the extrapyramidal system (the other to presumed cerebellar function)(164;165). The existence of such sub-dimensions could obscure relationship between antipsychotic medication and SNS. In conclusion, it is not possible to exclude the possibility that antipsychotic medication contribute to SNS expression. In any study that involves medicated patients, this possibility needs to be considered in the interpretation of the findings. Simply removing the possibility of a linear relationship (such as by covariance procedures) does not adequately address the problem.

Cognitive function as contributor to SNS

The key question is whether SNS expression could be considered as secondary to cognitive processes such as attentional impairment. The extent and nature of overlap between cognition and SNS has been explored in detailed in Chapter 6. The data suggest that while there are overlaps between SNS and cognitive function such as visual memory, much of the variance in SNS could not be explained by cognitive functions (including intelligence level). It is also noteworthy that the examination of SNS involves relatively simple instructions and executions in comparison to most cognitive function tests. It is therefore difficult to consider SNS simply as an epiphenomenon secondary to cognitive function impairment. It is more helpful to consider SNS as parallel phenomena to cognition (which specifically taps certain motor functions).

In this connection, there may be a difference between motor coordination signs and

sensory integration signs. As shown in the data reported here, a wider spectrum of cognitive function is involved in sensory integration, as compared with a more circumscribed set of associated cognitive function in relation to motor coordination signs. Given the suggestion that the nosological specificity of SNS is likely to be more related to motor coordination signs(67), it is important to examine what cognitive processes are likely to be involved in the motor SNS and to study the extent to which motor SNS taps similar variance in this cognitive domains. Studies in the relationship between cognition and SNS are still in its formative stage, and few consistent results have emerged. Of the candidate functions in this data set, visual working memory (immediate memory) is a candidate that remains consistently related to motor SNS in two independent cohorts in the current data set. It is important to examine in more detail the component processes in the visual memory task in order to further delineate the relationship. It is noteworthy that in the current data set, the relationship between cognition and SNS only become apparent after treatment of the first episode and not at the presentation of the first episode. This observation also raised the possibility that medication may mediate the relationship between cognitive function and SNS.

Measurement limitations and suggestions for future SNS evaluation

This dissertation described data that together with the existing literature clearly indicate a role for SNS as a potential target feature in schizophrenia research. The

relationships between SNS and a number of demographic, clinical and cognitive areas are becoming increasing clarified. However as research questions are becoming more focused, detailed and demanding, expectations on measurement sensitivities in future studies will also increase. In this context it appears appropriate to end the dissertation with a critical review of the current strategy in the evaluation of SNS with an aim of suggesting further refinements.

Although the commonly applied SNS inventories are operationized and standardized, and in general achieve good interrater reliabilities, there are several limitations. Some of the issues have been presented in Chapter 1. They will be further developed here.

Individual signs are rated on a categorical basis, usually on no more than three points (i.e. absent, present, severe), and very often can only be rated for either present or absent. Given that fact that SNS are present in a substantial proportion of patients and controls, the distribution of the underlying abnormality should be conceived as a continuous variable. Reduction to a categorical rating could result in a lost of quantitative information which render the severity grading of a SNS scale less sensitive in relation to the putative underlying disturbance.

The nature of abnormality embedded in an individual sign is likely to be multi-dimensional, in fact this can be inferred from certain description of SNS ratings, for example, in finger tapping or opposition, there may be loss of rhythm, or abnormal movement trajectory. Either abnormality could cause a sign to be rated positive. Thus

in current SNS methodology multi-dimensional information are being compressed into one dimension.

There may be duplication of information in different SNS items. Several SNS are very similar to one another e.g. finger thumb opposition and finger tapping. Abnormalities underlying one of the signs might be very similar to those underlying another. Though it could be argued that they may represent different difficulties level, yet the rationale has not been explicitly examined. Adding up information from similar signs may inflate the importance of one type of abnormality.

The use of summative scores for subscale is very common in data analysis. This is related to the fact that individual signs are usually categorically rated, and the number of signs is usually relatively large in relation to sample size. Thus the use of summative scores for subscales reduces the number of variables as well as provides a score that better approximates a continuous variable. Yet the practice of adding up scores of individual signs has certain limitations. In the process of summation, the separate importance of number and severity of signs are lost.

In view of these limitations, attempts should be made to construct a more refined approach to the assessment of neurological signs in terms of exploration of the underlying dimensions. Some of these dimensions could be more sensitively measured. Redundant signs addressing the same dimensions could also be reduced. This would result in the measurement of a fewer number of signs, each producing

data on several dimensions.

Some studies have addressed motor dysfunction in schizophrenia with more detailed assessment of motor system abnormalities, for example using reaction time, or kinematic measures. This approach may enrich the study of SNS. However, currently, most motor function studies use separate motor paradigms unrelated to SNS. Studies using quantitative instrumental measure to evaluate motor paradigms that *are closely related to SNS* could bridge the current gap and enable an examination of the underlying dimensions of SNS.

Appendix

Appendix 1 Clinical Centres involved in the Research Programme

Abbreviation	Clinical centre	Location	Service nature	Studies involved
FH	Fulbourn Hospital	Cambridge UK	Rehabilitation Unit for Chronic inpatients	Study 2
QMH	Queen Mary Hospital	Hong Kong Island, Hong Kong	Acute inpatient unit and outpatient unit	Study 1 and 4
KCH	Kwai Chung Hospital	Kowloon, Hong Kong	Acute inpatient unit, rehabilitation unit for chronic inpatients	Study 1
LCKH	Lai Chi Kwok Hospital	Kowloon, Hong Kong	Rehabilitation unit for chronic inpatients	Study 1 and 3
PYNEH	Pamela Youde Nethersole Eastern Hospital	Hong Kong Island, Hong Kong	Acute inpatient unit and outpatient unit	Study 4

Appendix 2: CNI SNS subscales

Subscale score calculation

Seven subscales are defined in the CNI (see item description below). 3 of the subscales concern SNS. 10 items can be scored on both left and right (LR), each is treated as an independent score. Scaled subscale score is the summed score for the subscale items divided by the maximum possible score, and then converted to a 0 to 100 scale (i.e. percent maximum score). For the purpose of subscale score calculation, scores of 0.5 are treated as 0; and scores of 2 are treated as 1.

THE CAMBRIDGE NEUROLOGICAL INVENTORY (CNI)

An instrument for further clinical examination of psychiatric patients

OVERALL TESTING PROCEDURES

PART 1

* *Assessment of speech*
* *Assessment of eye movements*
* *Assessment of cranial nerves*
* *Extremity examinations (tone, strength, reflex)*

PART 2

* *Soft sign examinations (primitive reflexes; repetitive movement; sensory integration)*

PART 3

* *Assessment of posture and movements (including catatonia and tardive dyskinesia)*

Equipment required: tendon hammer, tongue depressor, pen, torch, a set of 5-10 small commonly encountered objects (coin, paper clip, match, eraser, rubber band, screw, battery, shell, and button).

Instruction: Enter rating in [ ] space provided.
Enter additional remarks in the following space [ ]
Unless otherwise specified rate as follows:

0	*Normal*
0.5	*Subthreshold*
1	*Definitely abnormal*
2	*Grossly abnormal*
8	*Unable to perform/attempt any part of task despite adequate comprehension and cooperation*
9	*Missing. Or unable to test, lack of cooperation or comprehension*

(Additional description can be entered next to rating in the space provided. Additional information is advisable if ratings 0.5, 8 or 9 are selected. Do not use rating "2" if a test can only be either positive or negative)

PART I

SPEECH

Patient is engaged in casual conversation for up to 3 minutes. Introduction to the examination and instruction to relax are given.

ARTIC POOR ARTICULATION
Poor articulation
Rate during 3 minutes of casual conversation.

0 Normally understandable
1 Patient must repeat to be understood on several occasions
2 Almost incomprehensible

0 0.5 1 2 8 9 [ ] [ ]

APROS APROSODIC SPEECH

Simply unvarying, harsh or stereotyped inflections should not be rated unless marked. Eg. unnaturally loud, strident, high-pitched, or alternatively feeble, whispering or completely monotonous intonations. Occasionally also automaton-like, sing-song, rasping, strangled, or warbling inflections.

0 0.5 1 2 8 9 [ ] [ ]

UNINT UNINTELLIGIBLE SPEECH

Mumbling, non-social speech, not merely due to poor articulation. Do not rate mere incoherent speech due to thought disorder.
0 0.5 1 2 8 9 [ ] [ ]

"I am going to test your eyes next."

ASSESSMENT OF EYE MOVEMENTS

There are two main components, smooth pursuit eye movements and saccadic eye movements. Each of the two components should be conducted en block and ratings completed afterwards.

SMOOTH PURSUIT EYE MOVEMENTS

Patient asked to focus on a slowly moving target (a pencil or pen) at a distance that the patient can focus on. Glasses are removed if present.
The target is moved slowly in a horizontal and then a vertical direction.

"Could you follow the (eg. pen) with your eyes, keeping the head still."

EXT SPM EXTENT OF SMOOTH PURSUIT EYE MOVEMENTS

Rate as positive if range of movement restricted

0 0.5 1 2 8 9 [ ] [ ]

SMO SPM SMOOTHNESS OF SMOOTH PURSUIT EYE MOVEMENTS

Rate as positive if noticeably catchy or jerky

0 0.5 1 2 8 9 [ ] [ ]

IPR GZ GAZE IMPERSISTENCE
Patients asked to fix his/her gaze on an object(eg. a pen) at a 45' angle in the horizontal plane of the right and then left visual fields for 15 sec each.

"Could you keep looking at this (pen) with your head still, until I tell you to stop."

0 No deviation from fixation
1 Deviation from fixation but able to resume gaze
2 Deviation from fixation repeatedly, unable to resume gaze

0 0.5 1 2 8 9 [ ] [ ]

SACCADIC EYE MOVEMENTS

Hold one target at the right extreme of lateral vision, and the other target at the left extreme of lateral vision. Patient is asked to look at one of the targets and then quickly at the other-AS FAST AS POSSIBLE, to and fro for several times. Observe for smoothness of movement, presence of blinking and head movement.

"Could you look at the (pen)... and then at this (torch)... and back to the (pen). Do this a few times as quickly as you can."

SC SMO SMOOTHNESS OF SACCADE MOVEMENTS
0 One smooth movement
1 Slight jerky movements
2 Extremely jerky movement

0 0.5 1 2 8 9 [ ] [ ]

SC BLK BLINK SUPRESSION DURING SACCADES
Blinking is observed during two L-R saccades.

"I notice you tend to blink while you do this, see if you could do it without blinking."

0 No blinks
1 Unable to stop blinks on some (more than two but not all) occasions
2 Unable to stop blinks on all saccades

0 0.5 1 2 8 9 [ ] [ ]

SC HEAD LATERAL HEAD MOVEMENTS DURING SACCADES

"You tend to move your head when you do this, see if you could do it without moving the head."

0 None
1 Head moves with eyes, unable to suppress on some (more than two but not all) occasions
2 Head moves with eyes on all occasions

0 0.5 1 2 8 9 [ ] [ ]

ASSESSMENT INVOLVING THE HEAD REGION

This part could be completed and scored either item by item or en block, depending on the examiner's familiarity with the assessment.

WINK WINK WITH OTHER EYE OPEN
"Could you wink with the other eye open, like this"
(Demonstrate)
If lateralized, indicate the side in which unilateral blinking is difficult

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

GLAB GLABELLAR TAP
Patient instructed to fix his/her gaze on a point across the room. After explanation, the patient is approached from above the forehead outside of the visual field, and the examiner taps the glabellar region 10 times with the index finger.

"I am going to tap your forehead gently. Just try to relax and look ahead at the (fixation point or object)."

0 One to three blinks (include partial blinks)
1 More than three blinks
2 No habituation at all

0 0.5 1 2 8 9 [ ] [ ]

RAP TN RAPID TONGUE MOVEMENTS
Demonstrate. Touch corners of mouth with tongue alternately.

"Could you stick the tongue out and move it as quickly as you can between the two corners of the mouth."

0 Normal, (>4 touches / second)
1 Slow, (<4 touches / second)
2 Very slow or dysrhymic

0 0.5 1 2 8 9 [ ] [ ]

IPR TN IMPERSISTENCE-TONGUE PROTRUSION

Hold tongue out (without using the teeth) for 15 sec.

"Could you keep the tongue out until I tell you to stop?"

0 Maintains act for 20 seconds
1 Pulls tongue in before 20 seconds, but able to resume test
2 Pulls tongue in before 20 seconds and unable to complete test

0 0.5 1 2 8 9 [ ] [ ]

"I am going to examine your arms next."

EXTREMITY EXAMINATIONS

These examinations of tone, strength and reflexes in the upper and lower limbs are performed en block with the patient seated.
Scores are entered on page after the blocks of examination.

UPPER LIMB EXAMINATION

TON UL+/- UPPER LIMB TONE

Flexion-extension, pronation-supination of the elbow joint; and flexion-extension of the wrist joints are examined. The degree of resistance from normal to extreme rigidity is scored.

"Could you relax and let your arms go as soft as possible while I hold it."

(e.g. for increased tone)
0 Normal
1 Slight to moderate stiffness and resistance
2 Marked rigidity with difficulty in passive movement

STR UL UPPER LIMB STRENGTH

"Could you grasp my fingers as hard as you can?"
"Could you pull me towards you?"

0 Normal
1 Decreased

DTR UL+ UPPER LIMB HYPERREFLEXIA
Rating for all reflex items

0 Normal
0.5 Equivocal

1 Positive
9 Missing

DTR UL- UPPER LIMB HYPOREFLEXIA

"I am going to examine your legs now. Could you take off your shoes and socks?" (This is a good point to observe ambitendence but the rating can be enter later: Part 3)

LOWER LIMB ASSESSMENT

0 Normal (skip, end of Part 1)
1 Abnormality present (rate following items)

TON R/L LL+/- LOWER LIMB TONE
0 Normal
1 Definitely increased or decreased
2 Grossly increased or decreased

STR LB LOWER LIMB STRENGTH

"Could you straighten your leg?"
"Could you point the toes towards you?"

0 Normal
1 Decreased

DTR LL+ LOWER LIMB HYPERREFLEXIA

DTR LL- LOWER LIMB HYPOREFLEXIA

EXTREMITY EXAMINATION RESULTS

	TONE	STRENGTH	REFLEX
UPPER LIMB INCREASED			
UPPER LIMB DECREASED			
LOWER LIMB INCREASED			

LOWER LIMB DECREASED			

PTR EXTENSOR PLANTER REFLEX

0 Normal
0.5 Equivocal
1 Extensor

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

END OF PART 1

This is a good point to allow the patient to have a short break before proceeding to Part 2. "Would you like to take a break for a little while?"

PART 2

SOFT SIGNS ASSESSMENT

There are mainly three groups, the first group of soft sign tests are some "primitive reflexes". The second group concerned with repetitive sequential motor execution. The third group are tests related to integration of sensory information.

Patient is seated facing the examiner (seated opposite). Each test is performed and rated before going on to the next test.

SNOUT SNOUT REFLEX
After explanation, patient is instructed to relax, and the examiner rests a tongue depressor against the patient's philtrum and taps gently with the index finger.

"Could you close your eyes and relax. I am going to tap gently on your mouth."

0 No contraction of the orbicularis orris
1 Any contraction of the orbicularis orris

0 0.5 1 2 8 9 [ ] [ ]

GRA GRASP REFLEX

Patient is instructed to relax and the palm is stroked lightly with the examiner's index finger. The sign should be demonstrable at least twice on repetition

0 No movement of patient's hand
1 Some flexion of fingers
2 Examiner's finger grasped

0 0.5 1 2 8 9 [ ] [ ]

P-M PALMOMENTAL REFLEX

The patient is instructed to relax. Muscle activity around the lips is observed. Then the thenar eminance is stroked vigorously with a blunt pointed object. Induced movement of the mentalis muscle is observed.

"I am going to stroke the palm. Could you close your eyes and relax."

0 No movement observed
1 Movement of the mentalis muscle

0 0.5 1 2 8 9 [ ] [ ]

FG NOS FINGER-NOSE TEST

Patient is instructed to close eyes and touch the tip of his/her nose with the tip of his/her index finger.

"Could you close your eyes and touch your nose with this finger." (patient's index finger touched)

0 No intention tremor or passpointing
1 Mild intention tremor or passpointing
2 Marked intention tremor or passpointing

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

FGTHTAP FINGER-THUMB TAPPING

Patient asked to touch tip of thumb with tip of index finger as quickly as possible

"Could you do this (demonstrate), now start."

0 Normal
1 Minor mistakes, slow or clumsy, but no major disruption of movements
2 Major disruption or repeated breakdown of sequence

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

FG TH FINGER-THUMB OPPOSITION

Patient asked to place both hands palm up with fingers fully extended on his/her legs. The patient is to start with his/her dominant hand and is to touch the tip of his/her fingers with the tip of his/her thumb, from index finger to little finger, returning to index finger, for a total to 10 repetitions.

"Now could you do this (demonstrate) and carry on 10 times. Start now." (Observe for mirror movement)

0 Normal
1 Minor mistakes, slow or clumsy, but no major disruption of movements
2 Major disruption or repeated breakdown of sequence

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

MIRROR1 MIRROR MOVEMENTS

The patient's hand, which is not performing the Finger-Thumb Opposition Test, is observed for mirror movements (tendency for the resting hand to move in a way symmetrical to the performing hand)

0 No observable movement
1 Minor movements of the fingers
2 Consistent, distinctive movements of the fingers

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

DIADOCK DIADOCHOKINESIS

The patient is asked to make a fist with one hand and pat the back of the fist with the other hand alternately using the palm and the dorsum.
Demonstrate 5 times, rate as FG TH

0 Normal
1 Minor mistakes, slow or clumsy, but no major disruption of movements
2 Major disruption

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

MIRROR2 MIRROR MOVEMENTS

The patient's resting hand, holding a fist, is observed for mirror movements

0 No observable movement
1 Minor pronation or supination movements
2 Consistent, distinctive pronation and supination movements of the forearm

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

FEP FIST-EDGE-PALM TEST

The patient is shown the task and then asked to perform the following: using a smooth and steady rhythmic pattern, to touch the table with the side of his/her fist, the edge of his/her hand, and the palm of his/her hand. The patient is to break contact with the surface of the table between each change in hand position, but not to bring the arm back in full flexion. The patient is to repeat this sequence of position changes 10 times.

"Watch me do this."
Demonstrate 5 times, without verbal instruction
"Now see if you could do it." (Repeat demonstration once if patient fails to perform)

0 Normal
1 Minor mistakes, slow or clumsy, but no major disruption of movements
2 Major disruption or repeated breakdown of sequence

L 0 0.5 1 2 8 9 [ ] [ ]
R 0 0.5 1 2 8 9 [ ] [ ]

OZE OZERETSKI TEST

Patient is to place both hands on the table, one hand palm down and the other hand in the shape of a fist. The patient is then asked to simultaneously alternate the position of his/her hands in a smooth and steady motion. The patient is asked to repeat this motion 15 times.

"Watch me do this."
Demonstrate 5 times.
"Now see if you could do it" (repeat demonstration once only if patient fails to perform)

0 Normal
1 Minor mistakes, slow or clumsy, but no major disruption of movements
2 Major disruption or repeated breakdown of sequence

0 0.5 1 2 8 9 [ ] [ ]

RHY TAP RHYTHM TAPPING TEST

Ask the patient to reproduce exactly the series of taps heard while the patient has eyes closed.(5 trials using stimulus sequence suggested:)

"I am going to tap some sound on the table like this (demonstrate), Could you tap the same rhythm back to me? Now close your eyes and listen."

	STIMULUS SEQUENCE	RESPONSE
1	** ** **	
2	.* .* .*	
3	*.. *.. *..	
4	*... * *	
5	..* ..*	

0 No error
1 One error
2 Two or more errors

0 1 2 8 9 [ ] [ ]

GO-NOGO GO-NO GO TEST
Patient asked to tap the table once if the examiner taps the table once, but not to tap if the examiner taps the table twice. Give adequate demonstration and practice to ensure comprehension of task.
"If I tap once on the table like this (demonstrate), could you tap once. If I tap twice on the table like this (demonstrate), please do not tap."

STIMULUS	* *	*	*	* *	*
RESPONSE					

0 No error
1 One error
2 Two or more errors

0 1 2 8 9 [ ] [ ]

EXTINCT EXTINCTION

The patient is seated, with hands resting palm down, on his/her knees and with eyes closed. The patient is told that he/she will be touched on either the cheek, hand, or both, and is to say where he/she has been touched. If the patient names just one touch, he/she is asked (the first time this occurs only) if a touch is felt anywhere else. Simultaneous touching is performed in the following order: **right cheek-left hand, left cheek-right hand, right cheek-right hand, left cheek-left hand, both hands, and both cheeks.**
Intact sensation to touch is confirmed in each test area beforehand.
"I am going to touch your face and your hand like this (demonstrate). Could you tell me which side of the face and the hand I am touching? For example, (demonstrate). Now close the eyes."

STIMULU	***RIGHT CHEEK***	***LEFT CHEEK***	***RIGHT CHEEK***	***LEFT CHEEK***	***RIGHT HAND***	***RIGHT CHEEK***
STIMULU	***LEFT HAND***	***RIGHT HAND***	***RIGHT HAND***	***LEFT HAND***	***LEFT HAND***	***LEFT CHEEK***
RESPONS						

0 No error
1 One error
2 Two or more errors

0 1 2 8 9 [ ] [ ]

FG AGN FINGER AGNOSIA

With the patient facing the examiner, hands palm down on the table, fingers spread, eyes closed, two fingers are simultaneously touched. The patient is asked to state the number of fingers between the two touched. The answer may be 0, 1, 2 or 3. A total of 5 trials for each hand is tested.

"Could you put your hand on the table like this (demonstrate). I am going to touch two of the fingers like this (demonstrate). I'd like you to tell me how many fingers there are in between the ones that I am touching. For example, this will be...(demonstrate). Now close your eyes."

Test sequence: 1 for thumb, 5 for last finger etc.

LEFT HAND	**2 - 4**	**1 - 3**	**3.-.4**	**2.-.5**	**1.-.5**
RESPONSE					
RIGHT HAND	**1.-.3**	**2.-.4**	**1.-.4**	**2.-.3**	**1.-.5**
RESPONSE					

0 No error
1 One error
2 Two or more errors

L 0 1 2 8 9 [ ] [ ]
R 0 1 2 8 9 [ ] [ ]

STEREO STEREOGNOSIS

Patient, with eyes closed, is asked to identify an object placed in his/her hand. Patient is instructed to feel the object with one hand and to take as much time as needed. If the patient cannot name the object, he/she is asked to describe for what purpose the object is used. The patient starts with the dominant hand. 5 trials are conducted for each hand. Suggested objects (paperclip, coin, rubber band, eraser, screw, small seashell, match, etc)

"Could you close your eyes and tell me what this object is, just by feeling it."

0 No error
1 One error
2 Two or more errors

L 0 1 2 8 9 [ ] [ ]
R 0 1 2 8 9 [ ] [ ]

GRAPH GRAPHESTHESIA

The patient, with eyes closed, is asked to identify the number written on his/her palm with a blunt point, the number being orientated the right way up facing the patient. Five trials for each hand. Stimulus can be repeated once only upon request by the patient.

"I am going to trace a number on your palm, like this would be a (number). (Demonstrate). Could you tell me what the number is, with your eyes closed?"

LEFT HAND	**3**	**7**	**8**	**5**	**9**
RESPONSE					
RIGHT HAND	**2**	**4**	**0**	**3**	**6**
RESPONSE					

0 No error
1 One error
2 Two or more errors

L 0 1 2 8 9 [ ] [ ]
R 0 1 2 8 9 [ ] [ ]

L/R ORN LEFT-RIGHT ORIENTATION

(Examiner should remove wrist watch before the test)
Patient is asked to point to **his/her right foot, left hand; place his/her right hand to left shoulder, left hand to right ear; point to examiner's left knee, then right elbow; with examiner's arms crossed, point to examiner's left hand with his/her right hand, and with examiner recrossing arms, point to examiner's right hand with his/her left hand.**

"Could you point to ( ) with your ( )."

POINT TO	*YOUR RIGHT FOOT*	*YOUR LEFT HAND*	*YOUR LEFT SHOULDE*	*YOUR RIGHT EAR*	*MY LEFT KNEE*	*MY RIGHT ELBOW*	*MY LEFT HAND*	*MY RIGHT HAND*
WITH			*YOUR RIGHT HAND*	*YOUR LEFT HAND*			*YOUR RIGHT HAND*	*YOUR LEFT HAND*

0 No error
1 L/R disorientation confined to perception of another person

2 L/R disorientation in self body space

0 0.5 1 2 8 9 [ ] [ ]

END OF PART 2
Another break can be taken at this point.
"Would you like to take another break now?"

PART 3

POSTURE AND GAIT ASSESSMENT

These assessments are completed firstly with the patient seated, then standing up, and finally walking. The examinations are most conveniently completed en block before scores are entered. If the examiner is unfamiliar with the assessment, the examination could be divided into three smaller subunits (see below), each to be carried out as a block. It is important, however, that ratings for "global" items such as dyskinetic movements are entered after the examiner has observed the patient perform in all three blocks. The following sequence of examination is recommended:

Block A

1 Patient has been observed during the preceding parts of the assessment for global items such as perseveration, echopraxia, mutisum etc.

2 Patient seated in chair with hands on knees and legs slightly apart, and feet flat on the floor.(observe involuntary movement in the entire body)

3 Patient asked to sit with hands hanging unsupported, if male between legs, if female hanging over knees (observe involuntary movements in hands and body)

4 Patient asked to open mouth (observe involuntary tongue movement)

5 Patient asked to protrude tongue (involuntary movement observed)

6 Patient asked to tap thumb with each finger as rapidly as possible for about 15 seconds, first with the left and then the right hand.(observe facial and leg involuntary movements)

Block B

7 Patient asked to stand up (posture observed)

8 Patient asked to hold extended arms horizontally in front of them and then have the eyes closed.(observe pronator drift and Romberg's sign). Then the extended arms are moved to the side and instruction is given, with demonstration to drop the arms to the sides of the body (observe increased tone and imposed posture).

9 The examiner instructs the patient to let the arms go loose and then moves the patients arms into various positions, at times releasing support and note whether the arms drop freely (imposed posture and gegenhalten).

10 The examiner raises each of the patients outstretched arms in turn with one finger after instructing the patient to resist this.(test for mitgehen)

11 The examiner scratches his own head then pats his chest and legs after first instructing the patient to stand with his arms by his sides.(test for echopraxia)

Block C

12 Patient asked to balance himself for 15 seconds on each leg in turn.

13 Patient instructed to walk a few steps, stop and return (observe gait etc.)

14 Tandem walking (see item description)

GAIT INGAIT (EXAGGERATED ASSOCIATED MOVEMENT)

0 Absent
1 Definitely present
2 Markedly or pervasively present

0 0.5 1 2 8 9 [ ] [ ]

GAIT DEGAIT (REDUCED ASSOCIATED MOVEMENT)

0 0.5 1 2 8 9 [ ] [ ]

GAIT SL SLOW/SHUFFLING GAIT

0 0.5 1 2 8 9 [ ] [ ]

GAIT MN MANNERISTIC/BIZARRE GAIT

Mere clumsy or lumbering gaits should not be rated, and gait should be idiosyncratic rather than haunched, lordotic, shuffling etc. eg. constrained, mincing, over- precise; or alternatively extravagant, over-elaborate, featuring interpolated movements such as sidesteps and bowing. Also bizarre crablike, crouching or anthropoid gaits, and those with multiple, not easily described abnormalities.

0 0.5 1 2 8 9 [ ] [ ]

FACE DYS DYSKINETIC FACE AND HEAD MOVEMENT

Simple brief/dyskinesia-like
Do not rate tongue movements unless they also involve the mouth or the jaw.

0 0.5 1 2 8 9 [ ] [ ]

FACE SUS SUSTAINED FACE AND HEAD MOVEMENT

Simple sustained/ grimace-like
Do not rate tongue movements unless they also involve the mouth or the jaw
e.g. spasmodic facial contortions; should not be completely fixed

0 0.5 1 2 8 9 [ ] [ ]

FACE CX COMPLEX FACE AND HEAD MANNERISM/STEREOTYPY

Complex mannerism/stereotypy-like (usually of head; e.g. turning away, side-to-side looks, searching movements)

0 0.5 1 2 8 9 [ ] [ ]

GEGENH GEGENHALTEN

Resistance to passive movement which increases with the force exerted. Typically has a "springy" quality and appears automatic rather than willful. May be restricted to just one muscle group. Resistance increases with increasing force.

0 0.5 1 2 8 9 [ ] [ ]

MITG MITGEHEN

"Anglepoise lamp" raising of arm in response to light pressure, in the presence of an apparent grasp of the need to resist; should be demonstrable repeatedly. Severity of rating depends on the rapidity and apparent wish to anticipate the movement. Do not rate if understanding of instruction is poor.

0 0.5 1 2 8 9 [ ] [ ]

SP POSTR SIMPLE ABNORMAL POSTURE

Posture while standing

0 Normal
1 Somewhat stooped
2 Very stooped with downward gaze or rigid and extended

0 0.5 1 2 8 9 [ ] [ ]

CX POSTR COMPLEX ABNORMAL POSTURE

Mere ungainliness or slouching should not be rated.

0 Normal
1 e.g. assuming obviously abnormal hunched, constrained "closed" or alternatively exaggeratedly slack, over- relaxed positions when sitting; hugging sides, twisting legs round each other, sitting with torso forward but legs to one side in extremely uncomfortable way.

2 Marked or pervasive posturing. E.g. while sitting repeatedly hunching forward and rocking; while standing or walking striking a succession of poses.

0 0.5 1 2 8 9 [ ] [ ]

IM POSTR PERSISTENCE OF IMPOSED POSTURES

This is tested while testing tone of upper limb. If abnormality suspected, further testing of positioning the patient's limbs and releasing them is carried out.

0 Normal
1 Not sustained: tendency to retain limb positions passively imposed during testing for at least several seconds; this should be observed more than once.
2 Sustained "waxy flexibility"

0 0.5 1 2 8 9 [ ] [ ]

TK LB DYS DYSKINETIC TRUNK/LIMB MOVEMENT

Simple brief/dyskinesia-like (eg. stamping movements of legs, rocking trunk movements) Specify: random/ irregularly repetitive/ rhythmical/ tic- like; including rocking

0 0.5 1 2 8 9 [ ] [ ]

TK LB SUS DYSTONIC TRUNK/LIMB MOVEMENT

E.g. dystonic posturing of extremities, hyperpronation on arm raising, torsion movements

0 0.5 1 2 8 9 [ ] [ ]

TK LB CX TRUNK/LIMB MANNERISM/STEREOTYPY

More stereotypy-like: eg. rubbing the thumb over the forefinger, other kinds of finger play, touching, rubbing, stroking and patting various parts of the body especially the face. Also repeatedly turning the head away from the examiner, looking round distractedly throughout the interview, twisting one arm up behind the back whilst walking, repeatedly rising from chair and approaching examiner. More mannerism like: eg. holding arms in an unnatural crooked way, holding an arm out in a meaningless gesture, keeping one arm tucked under armpit.

0 0.5 1 2 8 9 [ ] [ ]

PRO PRONATOR DRIFT

Patient asked to hold two arms straight in front of him/her horizontally and close the eye. Downward drift of one or both of the arms is observed.

"Could you hold your arms out in front of you, like this (demonstrate). Now close your eyes and keep the arms in the same place."

0 0.5 1 2 8 9 [ ] [ ]

ARM ARM DROPPING

The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard and there is a slight, natural rebound as the arms hit the sides. If the sign is positive the arms falls very slowly:

"Now relax and let the arms drop to the sides like this (demonstrate)."

0 Normal, free fall with loud slap and rebound
1 Fall slowed with less audible contact and little rebound
2 Arms fall as though against resistance; as though through glue

0 0.5 1 2 8 9 [ ] [ ]

TREMOR TREMOR

0 0.5 1 2 8 9 [ ] [ ]

ROMBERG ROMBERG'S SIGN

Standing with eyes closed and feet together

0 Normally still or slight weaving
1 Widened base to stay in place
2 Unable to stand still with eyes closed

0 0.5 1 2 8 9 [ ] [ ]

BALANCE BALANCE ON ONE LEG

Stand on one leg with eyes open for 10 seconds

0 No difficulty
1 With great difficulty
2 Unable to perform

Rate irrespective of side

0 0.5 1 2 8 9 [ ] [ ]

WALK WALKING

Walking down the hall at least 5 paces

0 0.5 1 2 8 9 [ ] [ ]

STOP STOPPING ON COMMAND

0 0.5 1 2 8 9 [ ] [ ]

TURN PIVOT WHILE TURNING

0 0.5 1 2 8 9 [ ] [ ]

TANDEM TANDEM WALKING

Heel to toe for 10 paces

0 0.5 1 2 8 9 [ ] [ ]

ABURPT SM ABRUPT/RAPID SPONTANOEUS MOVEMENT

e.g. sudden gestures, acts carried out smartly, springs to attention when asked to stand

0 0.5 1 2 8 9 [ ] [ ]

SLOW SM SLOW/FEEBLE SPONTANEOUS MOVEMENT

Weak, languid, laboured movements

0 0.5 1 2 8 9 [ ] [ ]

EXAGG SM EXAGGERATED MOVEMENTS

Accompanied by flourishes/flurries of adventitious movements

0 0.5 1 2 8 9 [ ] [ ]

ITER SM ITERATIONS OF SPONTANEOUS MOVEMENTS

Gestures or mannerisms repeated over short space of time: eg. touching face then repeating this several times; manneristically smoothing hair, then repeating this with increasing force until striking head; touching ring finger on one hand (while alluding to ring being stolen), then doing the same on the other hand, then repeated the whole sequence.

0 0.5 1 2 8 9 [ ] [ ]

OTHER SM OTHER ABNORMAL MOVEMENTS

Specify: echopraxia/ blocking/ ambitendence; do not rate any other abnormalities than these

Blocking/ambitendence: In practice not easy to distinguish from one another. Eg. freezing in the act of sitting forward and remaining motionless grasping the arms of the chair for nearly a minute; extending arm when examiner's is proffered, the halting in mid-action and moving arm to one side; while walking, stopping, half-turning back, then continuing.

0 0.5 1 2 8 9 [ ] [ ]

MUTISM MUTISM

(1=less than 10 isolated words in whole interview, 2=no speech)
0 0.5 1 2 8 9 [ ] [ ]

NECKRIG NECK RIGIDITY

0 0.5 1 2 8 9 [ ] [ ]

OVERACT OVERACTIVITY
(Do not rate simple restlessness/ akasthisia; do not rate unless substantial)

Typically bizarre rather than resembling simple restlessness; akathisia should be excluded where suspected.
0 Absent
1 Continual motor unrest: eg crossing and uncrossing legs, looking round, half rising from the chair; executing unending series of manneristic actions, touching body, then clasping hands, then gripping the chair arm, etc.

2 Approaching catatonic excitement: in more or less constant motion, incessantly performing pointless actions which are reiterated, elaborated and transformed into one another: eg. touching cardigan, then moving hands up and down the edges, then unbuttoning it and buttoning it up again, followed by breaking off interview to clamber over the tables and chairs on the ward. Also full blown excitement: eg. patient who moved round and round the ward striking an endless series of quasi-symbolic poses.

0 0.5 1 2 8 9 [ ] [ ]

UNDERACT UNDERACTIVITY
(Do not rate it patient is clearly sedated/parkinsonian; do not rate unless substantial)
Some degree of abnormality is commonly observed and should not be rated unless very noticeable.

0 Absent
1 Sits abnormally still throughout the interview with hardly any postural shifts; slumped in chair; very passive.
2 Marked hypokinesia, generally with striking absence of postural adjustments: eg sitting perched on chair in same position throughout interview not turning head when addressed from different direction; always sitting in same place on ward with arms in praying position. Also full blown stupor if encountered.

0 0.5 1 2 8 9 [ ] [ ]

AUTO OBE AUTOMATIC OBEDIENCE
May take the form of exaggerated co-operation with instructed movements: eg when asked to lift a finger, whole arm raised; when arm reached for, whole body leant forward and turned towards examiner; holding out both hands when examiner's offered for shaking. Alternatively, spontaneous continuation of actions: eg flapping arms when asked to drop them to sides, actively continuing passive arm movements during examination for tone. Occassionally, complying with all requests to an extraordinary degree: eg patient who screwed up eyes when asked to close them; peered intently in caricatured way when asked to look out of window; when asked to keep head up while walking, proceeded across the room with neck hyperextended.

0 0.5 1 2 8 9 [ ] [ ]

NONCOMPL POOR/FEEBLE COMPLIANCE
Inability to perform requested actions not explicable in terms of poor understanding, general un-cooperativeness, blocking/ambitendence, or parkinsonism; often has a bizarre quality. Eg when raising arm, movement gradually dies away; carries out most instructions promptly but fails to comply with some; cannot seem to maintain arms outstretched; when asked to hold out arms only seems able to do so in half- hearted, crooked way; when asked to raise a finger, after some delay lifts thumb.

0 0.5 1 2 8 9 [ ] [ ]

AB BEH OTHER ABNORMAL BEHAVIOUR

Specify: negativism/ hypermetamorphosis
Do not rate any other abnormality than these
Negativism: Should always reflect concrete instances rather than indefinite attitude. Eg. pulling arm violently away whenever the examiner reaches for it, holding breath when asked to breathe deeply, shutting eyes tightly when approached with an ophthalmoscope, jumping up when asked to lie down. Also, taking off socks when told to put shoes on; getting up from customary reclining position and walking away whenever approached by examiner. Occasionally, domination of entire behaviour by bizarre contrariness: eg normally quiet patient who met attempts to examine him with immediate struggling and vilification; leant backwards when pulled forwards; refused to stand up, then refused to sit down again.
Hypermetamorphosis: Typically only seen in setting of marked overactivity. Eg. attention repeatedly drawn by specks, bits of fluff, etc. on the floor which are reached for and scrutinized; randomly approaching various objects including wastebasket, rummaging in it, extracting apple core and eating it.

0 Absent
1 Definitely present
2 Markedly or pervasively present

0 0.5 1 2 8 9 [ ] [ ]

ECHO ECHOPHENOMENA
Tendency to repeat the examiner's speech or mimic the examiner's action
Echopraxia: incomplete copying movements should not be rated, and exercise judgement as to whether patient is just trying to be helpful. As well as being merely copied, movements may be modified or amplified: eg. smoothing of hair substituted for examiner's scratching of head, echopraxic chest patting progressively exaggerated until patient pulling at his shirt.
Global rating for echo-phenomena

0 0.5 1 2 8 9 [ ] [ ]

PERSERV PERSEVERATION
Tendency to persist in a particular response after it ceased to be appropriate
Global rating for perseveration

0 0.5 1 2 8 9 [ ] [ ]

END OF EXAMINATION

Appendix 3 Individual SNS item scores

Appendix 3a: Study 1 SNS prevalence

Signs	Normal n=94	%	Patients n=195	%	Chi-Square	Signifance level
Motor coordination						
Finger-thumb tapping L	1	1.06	18	9.23	10.87	0.001
Finger-thumb tapping R	1	1.06	21	10.77	13.21	<0.0001
Finger-thumb Opposition L	10	10.64	41	21.03	4.71	0.033
Finger-thumb Opposition R	9	9.57	40	20.51	5.39	0.02
Dysdiadocokinesia L	6	6.38	26	13.33	3.21	ns
Dysdiadocokinesia R	3	3.19	21	10.77	9.07	0.002
Fist-edge-palm L	29	30.85	70	35.90	0.72	ns
Fist-edge-palm R	15	15.96	71	36.41	12.69	<0.0001
Ozereski sign	16	17.02	53	27.18	3.69	ns
Sensory Integration						
Extinction	0	0.00	7	3.59	6.05	0.048
Finger agnosia L	27	28.72	64	32.82	0.98	ns
Finger agnosia R	24	25.53	69	35.38	3.65	0.015
Stereognosis L	0	0.00	18	9.23	9.40	0.009
Stereognosis R	0	0.00	21	10.77	10.47	0.005
Graphaethesia L	0	0.00	53	27.18	10.86	0.004
Graphaethesia R	4	4.26	41	21.03	13.86	0.001
L-R disorientation	5	5.32	46	23.59	14.57	<0.0001
Disinhibition						
Saccade blink	12	12.77	65	33.33	13.90	<0.0001
Saccade head	14	14.89	51	26.15	4.71	0.035
Wink	30	31.91	50	25.64	1.25	ns
Mirror movement 1 L	9	9.57	13	6.67	0.76	ns
Mirror movement 1 R	5	5.32	6	3.08	0.87	ns
Mirror movement 2 L	1	1.06	7	3.59	2.85	ns
Mirror movement 2 R	3	3.19	12	6.15	3.01	ns
no-nogo test	3	3.19	37	18.97	16.44	<0.0001

Chi-square statistics computed with all rating categories. ns: $p > 0.05$.

Appendix 3b: Study 2 SNS prevalence

Signs	Normal n=80	%	Patients n=52	%	Chi-Square	Signifance Level
Motor coordination						
Finger-thumb tapping L	0	**0.00**	7	13.46	11.37	0.001
Finger-thumb tapping R	0	**0.00**	9	17.31	14.86	<0.0001
Finger-thumb Opposition L	5	**6.25**	31	59.62	45.25	<0.0001
Finger-thumb Opposition R	7	**8.75**	30	57.69	37.42	<0.0001
Dysdiadocokinesia L	5	**6.25**	19	36.54	19.44	<0.0001
Dysdiadocokinesia R	2	**2.50**	17	32.69	23.32	0.0001
Fist-edge-palm L	12	**15.00**	31	59.62	30.71	<0.0001
Fist-edge-palm R	7	**8.75**	31	59.62	42.18	<0.0001
Ozereski sign	8	**10.00**	33	63.46	47.56	<0.0001
Sensory Integration						
Extinction	1	**1.25**	14	26.92	21.57	<0.0001
Finger agnosia L	26	**32.5**	29	55.77	11.08	0.001
Finger agnosia R	23	**28.75**	28	53.85	12.51	0.001
Stereognosis L	6	**7.5**	18	34.62	17.56	<0.0001
Stereognosis R	8	**10**	14	26.92	8.31	0.016
Graphaethesia L	15	**18.75**	28	53.85	19.29	<0.0001
Graphaethesia R	11	**13.75**	25	48.08	20.19	<0.0001
L-R disorientation	14	**17.5**	20	38.46	7.24	0.009
Disinhibition						
Saccade blink	5	**6.25**	22	42.31	27.34	<0.0001
Saccade head	2	**2.50**	11	21.15	14.17	0.001
Wink	5	**6.25**	22	42.31	25.90	<0.0001
Mirror movement 1 L	7	**8.75**	2	3.85	1.19	Ns
Mirror movement 1 R	8	**10.00**	1	1.92	3.24	Ns
MIrror movement 2 L	2	**2.50**	4	7.69	1.96	Ns
Mirror movement 2 R	9	**11.25**	7	13.46	0.15	Ns
no-nogo test	1	**1.25**	3	5.77	2.64	Ns

Chi-square statistics computed with all rating categories. ns: $p > 0.05$.

Appendix 3c: Study 3 SNS prevalence

Signs	Baseline n=38	%	3 Year n=38	%	Chi-Square	p-value
Motor coordination						
Finger-thumb tapping L	7	18.42	10	26.32	0.68	ns
Finger-thumb tapping R	7	18.42	13	34.21	2.44	ns
Finger-thumb Opposition L	9	23.68	10	26.32	0.07	ns
Finger-thumb Opposition R	10	26.32	10	26.32	0.00	ns
Dysdiadocokinesia L	7	18.42	8	21.05	0.08	ns
Dysdiadocokinesia R	5	13.16	5	13.16	0.00	ns
Fist-edge-palm L	18	47.37	19	50.00	0.22	ns
Fist-edge-palm R	16	42.11	19	50.00	0.85	ns
Ozereski sign	14	36.84	19	50.00	1.34	ns
Sensory Integration						
Extinction	5	13.16	2	5.26	1.76	ns
Finger agnosia L	0	0.00	12	31.58	18.33	0.001
Finger agnosia R	9	23.68	11	28.95	1.21	ns
Stereognosis L	9	23.68	7	18.42	0.59	ns
Stereognosis R	6	15.79	5	13.16	0.11	ns
Graphaethesia L	6	15.79	14	36.84	5.15	0.034
Graphaethesia R	9	23.68	19	50.00	5.15	0.015
L-R disorientation	4	10.53	6	15.79	0.35	ns
Disinhibition						
Saccade blink	10	26.32	18	47.37	4.07	ns
Saccade head	11	28.95	23	60.53	8.56	0.005
Wink	13	34.21	21	55.26	3.41	ns
Mirror movement 1 L	1	2.63	4	10.53	1.93	ns
Mirror movement 1 R	0	0.00	3	7.89	3.12	ns
MIrror movement 2 L	1	2.63	3	7.89	1.06	ns
Mirror movement 2 R	2	5.26	5	13.16	1.42	ns
no-nogo test	5	13.16	9	23.68	0.51	ns

Chi-square statistics computed with all rating categories. ns: $p > 0.05$.

Appendix 3d: Study 4 SNS prevalence

	Initial presentation	
	Number	%
Snout reflex	0.00	0.00
Grasp reflex	1.00	1.47
Palmomental reflex	0.00	0.00
Finger-nose L	10.00	14.71
Finger-nose R	12.00	17.65
Finger-thumb tapping L	5.00	7.35
Finger-thumb tapping R	7.00	10.29
Finger-thumb Opposition L	14.00	20.59
Finger-thumb Opposition R	13.00	19.12
Mirror movement 1 L	3.00	4.41
Mirror movement 1 R	8.00	11.76
Dysdiadocokinesia L	5.00	7.35
Dysdiadocokinesia R	2.00	2.94
Mirror movement 2 L	2.00	2.94
Mirror movement 2 R	5.00	7.35
Fist-edge-palm L	25.00	36.76
Fist-edge-palm R	24.00	35.29
Ozereski sign	23.00	33.82

3d.2 Comparison of SNS prevalence between first episode psychosis patients and matched controls

	First episode psychsis N=68		Matched controls N=68			
	Number	%	Number	%	Chi-sq	p-value
Snout reflex	0.00	0.00	0.00	0.00		
Grasp reflex	1.00	1.47	0.00	0.00	1.01	ns
Palmomental relfex	0.00	0.00	0.00	0.00		
Finger-nose L	10.00	14.71	0.00	0.00	10.79	0.001
Finger-nose R	12.00	17.65	0.00	0.00	13.16	<0.0001
Finger-thumb tapping L	5.00	7.35	1.00	1.47	2.79	ns
Finger-thumb tapping R	7.00	10.29	1.00	1.47	4.78	0.029
Finger-thumb Opposition L	14.00	20.59	6.00	8.82	3.75	ns
Finger-thumb Opposition R	13.00	19.12	7.00	10.29	2.11	ns
Mirror movement 1 L	3.00	4.41	8.00	11.76	2.47	ns
Mirror movement 1 R	8.00	11.76	4.00	5.88	1.46	ns
Dysdiadocokinesia L	5.00	7.35	4.00	5.88	0.12	ns
Dysdiadocokinesia R	2.00	2.94	3.00	4.41	0.21	ns
Mirror movement 2 L	2.00	2.94	1.00	1.47	0.34	ns
Mirror movement 2 R	5.00	7.35	1.00	1.47	2.79	ns
Fist-edge-palm L	25.00	36.76	16.00	23.53	2.83	ns
Fist-edge-palm R	24.00	35.29	9.00	13.24	9.00	0.003
Ozereski sign	23.00	33.82	11.00	16.18	5.65	0.017

3d.3 Comparison between medication naïve, medicated cases and normal controls item scores

	Medication-naïve N=34		Recently-Medicated N=34		Matched controls N=68			
	n	%	n	%	n	%	Chi-sq	p-value
Snout reflex	0.00	0.00	0.00	0.00	0.00	0.00		
Grasp reflex	1.00	2.94	0.00	0.00	0.00	0.00	3.02	ns
Palmomental relfex	0.00	0.00	0.00	0.00	0.00	0.00		
Finger-nose L	4.00	11.76	6.00	17.65	0.00	0.00	11.66	0.003
Finger-nose R	7.00	20.59	5.00	14.71	0.00	0.00	13.89	0.001
Finger-thumb tapping L	3.00	8.82	2.00	5.88	1.00	1.47	3.10	ns
Finger-thumb tapping R	3.00	8.82	4.00	11.76	1.00	1.47	5.05	ns
Finger-thumb Opposition L	6.00	17.65	8.00	23.53	6.00	8.82	4.22	ns
Finger-thumb Opposition R	7.00	20.59	6.00	17.65	7.00	10.29	2.23	ns
Mirror movement 1 L	1.00	2.94	2.00	5.88	8.00	11.76	2.67	ns
Mirror movement 1 R	3.00	8.82	5.00	14.71	4.00	5.88	2.19	ns
Dysdiadocokinesia L	4.00	11.76	1.00	2.94	4.00	5.88	2.26	ns
Dysdiadocokinesia R	1.00	2.94	1.00	2.94	3.00	4.41	0.21	ns
Mirror movement 2 L	0.00	0.00	2.00	5.88	1.00	1.47	3.07	ns
Mirror movement 2 R	3.00	8.82	2.00	5.88	1.00	1.47	3.14	ns
Fist-edge-palm L	11.00	32.35	14.00	41.18	16.00	23.53	3.46	ns
Fist-edge-palm R	11.00	32.35	13.00	38.24	9.00	13.24	9.32	0.009
Ozereski sign	11.00	32.35	12.00	35.29	11.00	16.18	5.73	ns

Appendix 4 item inclusion in key SNS studies

Core SNS items

Scale	B	C	E	F	G	H	A	I	J	K	L
aprosodic speech		+ (C1)									
unintelligible speech		+ (C1)									
extent PM				+ (F1)		+ (H2)				+ (K2)	
smooth SPM				+ (F2)				+			
inpersist gaze				+ (F3)		+		+		+	
saccade smooth											
saccade blink							+				
saccade head						+ (H1)	+			+ (K1)	
wink							+				
glabellar tap						+				+	+
rapid tongue											
impersist tongue											
snout						+	+	+	+	+	
grasp			+			+	+	+		+	
palmomental			+				+	+			
finger-nose L				+	+	+	+	+		+	+
finger-nose R				+	+	+	+	+		+	+
finger-thumb tap L		+		+			+		+		
finger-thumb tap R		+		+			+		+		
finger-thumb opp L		+		+	+	+	+		+(J1)	+	+
finger-thumb opp R		+		+	+	+	+		+(J1)	+	+
Mirror 1 L		+			+	+	+			+	+
Mirror 1 R		+			+	+	+			+	+
diadockinesia L		+		+	+		+				
diadockinesia R		+		+	+		+				
mirror 2 L		+		+	+		+				
mirror 2 R		+		+	+		+				
fist-edge-palm L					+	+	+		+	+	+
fist-edge-palm R					+	+	+		+	+	+
ozeretsky					+	+	+		+	+	
rhythm tapping			+			+	+			+	
go no go stimulus							+				
extinction	+	+ (C2)	+	+ (F4)	+ (G1)	+	+	+		+	+
finger agnosia L							+				
finger agnosia R							+				
stereognosia L	+				+	+	+	+		+	+
stereognosia R	+				+	+	+	+		+	+
graphesthesia L	+	+			+	+	+	+		+	+
graphesthesia R	+	+			+	+	+	+		+	+
L-R orientation		+			+	+	+	+			+

		(C4)						
gait increased movt	+	+		+				
gait decreased movt	+	+		+				
gait shuffling	+	+						
gait manneristic	+	+						+ (L1)
stand		+ (C3)			+		+	
arm drift				+ (G2)				
arm dropping								+
tremor					+		+	+
Romberg						+		
balance L	+		+					+
balance R	+		+					+
tandem		+	+	+	+	+	+	+
persevation								
abrupt spontaneous movt								+

Other items

	B	C	E	F	G	H	A	I	J	K	L
foot taps, right and left		+									
hopping L,R		+									
running		+									
disminished hearing		+									
visual perseveration and spoken command			+								
conceptualization and follow difficult task			+								
mnestic disturbance			+								
complex motor acts			+								
imaginary acts			+								
oral apraxia			+								
blunt vs sharp discrimination			+								
two object test			+								
memory			+								
optokinetic nystagmus			+								
draw a face test			+								
failure to recognize anomolies			+								
visual fields			+								
optic gnosts			+								
optic agnosis			+								
rotation of arms				+							
spooning of wrists and hands				+							
rotation of legs				+							
manipulation of match sticks				+							
finger following				+							
visual motor coordination				+							
finger spreading during tongue portrusion				+							
Overflow movements during hopping				+							
perception items from Denhoff et al 1968				+							
auditory visual integration				+		+				+	
face and body asymmetries				+							
postural asymmetrics				+							
mixed laterality				+							

lateralizing signs	+				
rapid opening and closing of hands	+				
walking on outer sides of feet	+				
finger location (=?graphesthesia)	+				
standing heel to toe	+				
crouching on tiptoe	+				
fixate an object for 20s with break gaze	+				
adventitious overflow during stand		+		+	
handedness		+			+ (L2)
footedness		+			+ (L2)
eyedness		+			
memory		+		+	
suck reflex		+	+	+	
gait lower limb					+
heel to toe balance					+
tongue protrusion					+
salivation					+
drawing cube					+
drawing (2 sequential drawing)				+	
two point discrimination		+			
hypertonia reflex			+		
nuchocephalia reflex			+		
finger position			+		

Legend to Appendix 4

B: Joseph M. Rochford, Thomas Detre et al. Neuropsychological Impairments in Functional Psychiatric Diseases. Arch Gen Psychiatry vol.22 1970 p114-p119

C: Frederic Quitkin, Arthur Rifkin et al . Neurologic Soft Signs in Schizophrenia and Character Disorders. Arch Gen Psychiatry vol.33 1976 p845-p853

C1: tongue twister check pronouncation, C2 face hand, C3 adventuous overflow, C4 left right confusion

E: Stephen M. Cox, Arnold M. Ludwig. Neurological Soft Signs and Psychopatholgy I. Can J Psychiatry Vol 24 1979 668-673

F: Joseph Marcus, Sydney L. Hans et al . Neurological Findings in High-Risk Children: Childhood Assessment and 5-Year Followup Schizophrenia Bulletin vol.11 1985 p83-p100

F1 eye movement in different direction, F2 fixation on an object in different direction,F3 pursing an object in different directions, F4 simultaneous stimualtion of face and hands,

G: J Schroder, Ch. Reitz. M. Binkert, H.Sauer. Translated by D. Barber . Neurological Soft signs-Heidelberg manual

G1 face hand test, G2 arm holding test,

H: Robert W. Buchanan and Douglas W. Heinrichs. The Neurological Evaluation Scale (NES): A Structured Instrument for the Assessment of Neurological Signs in Schizophrenia. Psychiatry Research 1989 vol. 27 p335-p350

H1 synkinesis, H2 convergence

I: L A Flashman, M Flaum, et al. Soft signs and neuropsychological performance in schizophrenia. Am J Psychiatry, 153 (4), April 1996

J: M J Cuesta, et al. Neurological frontal signs and neuropsychological deficits in schizophrenic patients. Schizophrenia Research, 20, 15-20

J1 pinao test

K: Celso Arango, et al . Prediction of Neuropsychological performance by neurological signs in Schizophrenia. Am J Psychiatry 1999 vol.156(9) p1349-1357

K1: Sequencing of Complex Motor Acts K2: motor coordination K3: sensory integration K4: others

L: Marie-Odile Krebs, Anne Gut-Fayand, Marie-Chantal Bourdel et al. Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schiaophrenia. Schizophrenia Research vol 45 2000 p245-p260

L1 gait arm swinging, L2 lateral preference,

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